# A STUDY OF CHARACTERISTICS AND OUTCOME OF CARDIO RENAL SYNDROME IN HEART FAILURE

*Dissertation Submitted to*
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**M.D. (GENERAL MEDICINE) BRANCH – I**


GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL
CHENNAI

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# CERTIFICATE

This is to certify that this dissertation entitled "A STUDY OF CHARACTERISTICS AND OUTCOME OF CARDIO RENAL SYNDROME IN HEART FAILURE" submitted by **Dr. JISHANTH M,** to the Tamil Nadu Dr. M.G.R. Medical University Chennai is in partial fulfillment of the requirement for the award of M.D. DEGREE BRANCH –I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.

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|---|---|
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# DECLARATION

I solemnly declare that the dissertation titled "A STUDY OF CHARACTERISTICS AND OUTCOME OF CARDIORENAL SYNDROME IN HEART FAILURE" was done by me at Stanley Medical College and Hospital during 2008-2010 under the guidance and supervision of Prof. Dr. A. GOWRISHANKAR, M.D.

The dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirement for the award of M.D.DEGREE (BRANCH-I) in General Medicine.

Place : Chennai
Date : Dr. Jishanth M

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# CONTENTS

# INTRODUCTION

# INTRODUCTION

Heart failure is one of the leading causes of hospitalizations throughout the world. Prevalence is 1% between the ages of 50 and 59 years, progressively increasing to >10% over age of 80 years. Concomitant and significant renal dysfunction is common in patients with heart failure.

Increasingly, the syndrome of heart failure is one of the cardiorenal failure, in which concomitant cardiac and renal dysfunctions exist, with each accelerating the progression of the other. One fourth of patients hospitalized for the treatment of acute decompensated heart failure will experience significant worsening of renal function, which is associated with worse outcomes.

It remains unclear whether worsening renal function specifically contributes to poor outcomes or whether it is merely a marker of advanced cardiac and renal dysfunction. Diuretic resistance, with or without worsening renal function, is also common in acute decompensated heart failure, although the definition of diuretic resistance, its prevalence, and prognostic implications are less well defined [(1)].

The term *cardiorenal syndrome* has been variably associated with cardiorenal failure, worsening renal function, and diuretic resistance but is more comprehensively defined as a state of advanced cardiorenal dysregulation manifest by one or all of these specific features.

The pathophysiology of the cardiorenal syndrome is poorly understood and likely involves interrelated hemodynamic and neurohormonal mechanisms. When conventional therapy for acute decompensated heart failure fails, mechanical fluid removal via ultrafiltration, hemofiltration, or hemodialysis may be needed for refractory volume overload. While ultrafiltration can address diuretic resistance, whether ultrafiltration prevents worsening renal

function or improves outcomes in patients with cardiorenal syndrome remains unclear. Newer therapeutic agents, including nesiritide, vasopressin antagonists and adenosine antagonists, hold promise for the future, and clinical trials of these novel agents are underway.

# AIM OF THE STUDY

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To do a cross sectional study on the prevalence, predictors and short term outcome in patients with heart failure and cardiorenal dysfunction(cardiorenal syndrome) with regard to variations in

Demographic characteristics

Etiologic factors

Severity of cardiac dysfunction

Associated risk factors

Treatment factors and

Outcome difference during hospital stay and 2 month follow up

# REVIEW OF LITERATURE

# REVIEW OF LITERATURE

The term *cardiorenal syndrome* has been variably defined but can be considered as a state of advanced cardiorenal dysregulation manifest by one or more of three specific features, including heart failure with concomitant and significant renal disease (cardiorenal failure), worsening renal function (developing during the treatment of acute decompensated HF), and diuretic resistance (Table 1)[1].

| | |
|---|---|
| **Cardiorenal failure** | Mild: HF + eGFR 30–59 mL/min/1.73 $m^2$<br>Moderate: HF + eGFR 15–29 mL/min/1.73 $m^2$<br>Severe HF + eGFR <15 mL/min/1.73 $m^2$ or Dialysis<br>Worsening renal function during treatment of ADHF<br>Change in creatinine >0.3 mg/dL or >25% baseline |
| **Diuretic Resistance** | Persistent congestion despite<br>>80 mg furosemide/day<br>>240 mg furosemide/day (continuous furosemide infusion)<br><br>Combination diuretic therapy (loop diuretic + thiazide + aldosterone antagonist) |

**Table 1: Features of Cardiorenal Syndrome**

The strong connection between renal and cardiovascular disease reflects the complex interactions between heart and kidneys. Arthur Guyton first extensively described normal physiological interactions between the control of extracellular fluid volume by the kidney and systemic circulation by the heart [2]. However, the pathophysiological mechanisms underlying this reciprocal relationship between the heart and the kidneys are still ambiguous. A diseased heart has numerous adverse effects on kidney function, while in parallel, renal

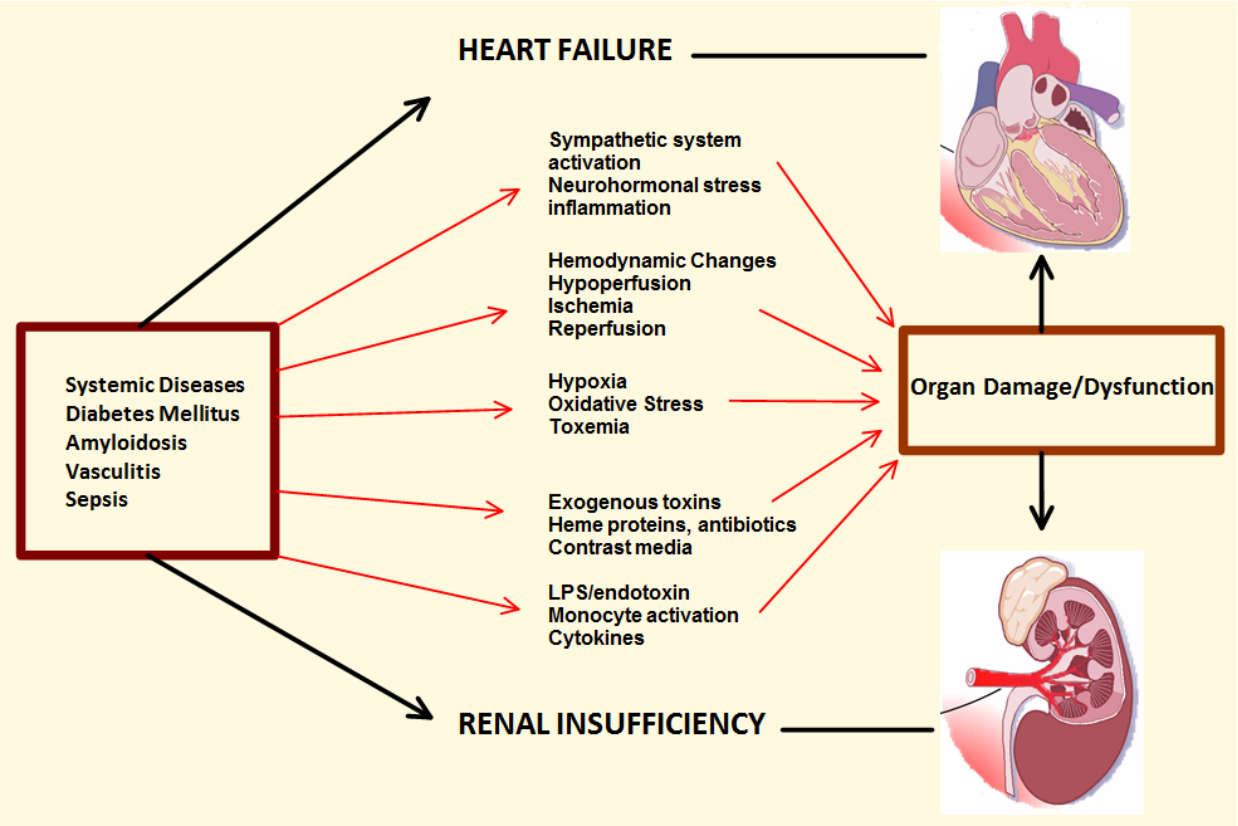
dysfunction can significantly impair cardiac function [3]

The so called cardiorenal syndrome is defined as a pathophysiological disorder of the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. This syndrome has recently been classified into 5 types[4].

**TYPE 1 CARDIORENAL SYNDROME** is the most common and is characterized by a rapid worsening of cardiac function (pulmonary edema, acutely decompensated chronic heart failure, cardiogenic shock, and predominant right ventricular failure), leading to acute kidney dysfunction. In this setting, acute kidney injury is more severe in patients with impaired left ventricular ejection fraction compared with those with preserved left ventricular function, having an incidence >70% in patients with cardiogenic shock. Early diagnosis of acute kidney injury remains a challenge and novel biomarkers have shed light in this direction.

Neutrophil gelatinase-associated lipocalin (NGAL) appears to be one of the earliest markers detected in the blood and urine of humans with acute kidney injury in different clinical settings, including contrastinduced nephropathy. Notably, in these patients with acute renal dysfunction, an increase in creatinine levels is observed only 48 to 72 hours after detection of NGAL.[5] Furthermore, cystatin C appears to be a better predictor of glomerular function than serum creatinine in patients with chronic kidney disease, because its blood levels are not affected by age, gender, race, or muscle mass.[6] Cystatin C also predicts acute kidney injury at 12 hours, although NGAL outperformed cystatin C at earlier time points. Considering them together, they represent a combination of structural and functional damage to the kidney.

## PATHOPHYSIOLOGICAL INTERACTIONS BETWEEN HEART AND KIDNEY




**Adapted from The AJCCVol 52 No:19, 2008 State-of-the-art Paper: Cardiorenal Syndrome**

**TYPE 2 (CHRONIC) CARDIORENAL SYNDROME** is characterized by chronic abnormalities in cardiac function causing progressive renal dysfunction, with a prevalence around 25%. Independent predictors of worsening renal function include old age, hypertension, diabetes mellitus, and acute coronary syndromes [(7)].

Hypoperfusion alone cannot explain the pathophysiology of renal dysfunction in this type of cardiorenal syndrome. The ESCAPE trial found a significant relation between right atrial pressure measured during pulmonary artery catheterization and serum creatinine, indicating the important role of renal congestion[(8)].

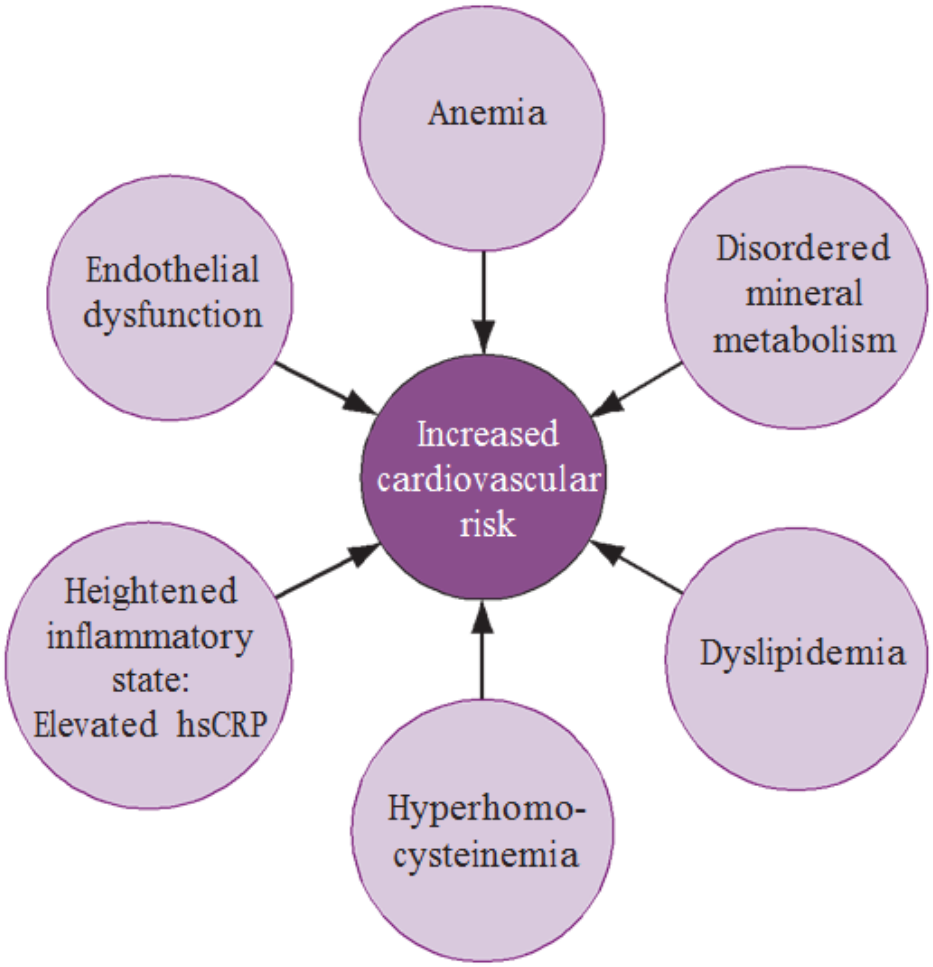
**TYPE 3 ACUTE RENO CARDIAC SYNDROME**, less common than type 1, is characterized by an abrupt and primary worsening of kidney function, leading to acute cardiac dysfunction (e.g. heart failure, arrhythmia, ischemia). Based on the RIFLE consensus definition (risk, injury, failure; loss; end-stage kidney disease), acute kidney injury has been identified in 9% of hospital patients and in 35% of ICU patients.[9] Mechanisms underlying impairment of cardiac function through acute kidney injury include fluid overload leading to pulmonary edema, hyperkalemia causing arrhythmias, and uremia affecting myocardial contractility. Finally, renal ischemia itself may precipitate activation of inflammation and apoptosis at the cardiac level.

**CHRONIC RENOCARDIAC SYNDROME (TYPE 4)** is characterized by a condition of primary chronic kidney disease contributing to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/ or increased risk of adverse cardiovascular events. According to current diagnostic criteria for chronic kidney disease, at least 10% of the general adult population suffers from this major public health problem [10].

More than 50% of deaths in end-stage renal disease cohorts are attributed to cardiovascular disease. In addition, patients with severe forms of chronic kidney disease have a 10 to 20-fold increased risk of cardiac death compared to the general population, while even less severe forms of chronic kidney disease may be associated with significant cardiovascular risk[11], documenting an inverse relationship between renal function and adverse outcome (consistently occurring at estimated glomerular filtration rate levels <60 ml/min/1.73m$^2$). In this context, data derived from our institution show that parallel cardiac and renal involvement in hypertensive individuals without overt cardiovascular disease is associated with

a very high risk of future cardiovascular events.[12] Part of this increased risk in patients with chronic kidney disease is attributed to under-treatment and less chance to receive risk-modifying interventions. Potential reasons for this sub-therapeutic performance include concerns about further worsening of renal function, and/or therapy-related toxic effects due to low clearance rates.

## Additional Risk Factors for Cardio-Vascular Disease in Patients with Renal Disease



Finally **SECONDARY (TYPE 5) CARDIORENAL SYNDROME** is characterized by the presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders. In the acute setting, severe sepsis represents the most common and serious condition that can affect both organs.

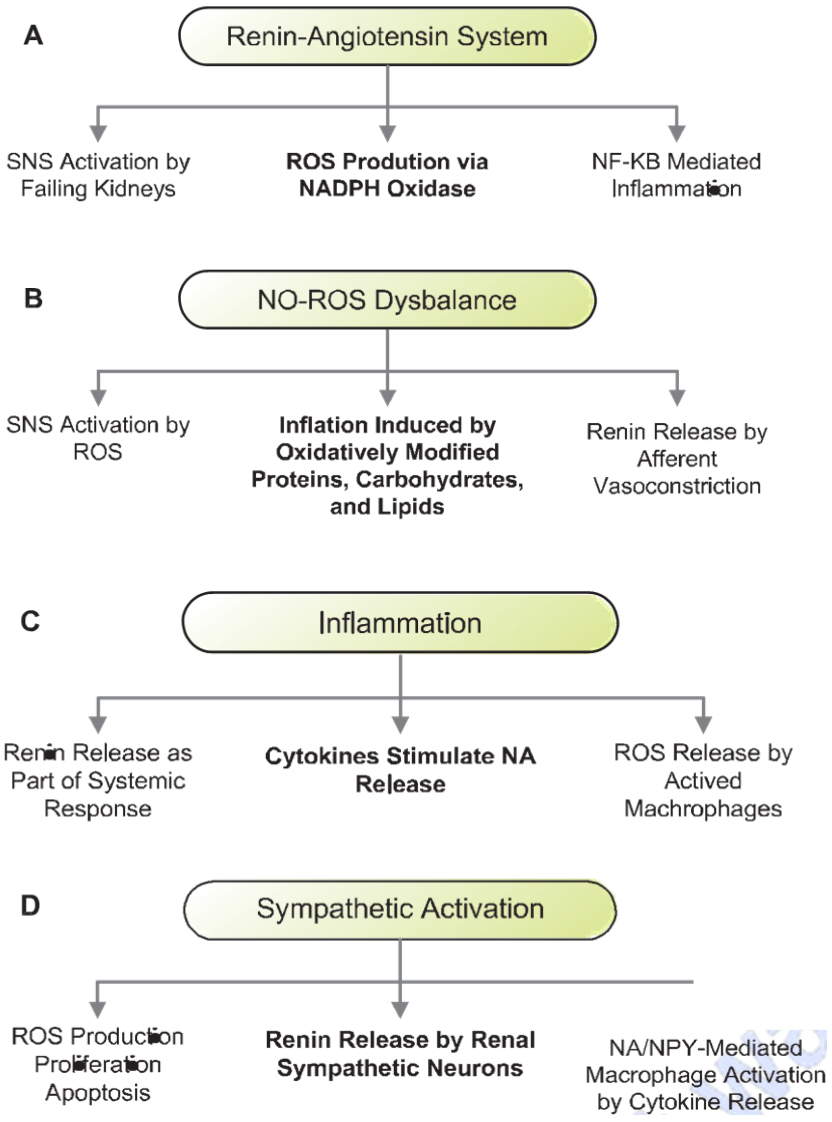
Necessary to offer the best therapy to these patients demands a multidisciplinary approach, combining the expertise of cardiology, nephrology, and critical care, as was highlighted in the recent international symposium on "Renal dysfunction and cardiovascular diseases 2010" that took place in Athens. In conclusion, more attention needs to be paid to reducing risk factors for the cardiorenal syndrome.

**Classification of cardiorenal syndrome proposed by Ronco and colleagues** [13]

| Type | Name | Mechanism | Clinical Conditions | Markers* |
|---|---|---|---|---|
| Type I | Acute Cardiorenal syndrome | Abrupt worsening of kidney function leading to acute kidney injury | Acute cardiogenic shock and acutely decompensated congestive heart failure | ET-1 Troponin |
| Type II | Chronic Cardiorenal syndrome | Chronic abnormalities in kidney function causing progressive and potentially permanent kidney disease | Chronic congestive heart failure | ET-1, BNP |
| Type III | Acute Renocardiac syndrome | Abrupt worsening of kidney function causing acute cardiac disorder | Acute kidney ischemia and glomerulonephritis | TNF-α,IL-1 IL-6, IL-8 |
| Type IV | Chronic Renocardiac syndrome | Chronic kidney disease contributing to decline in cardiac function | Chronic glomerular and Interstitial disease | PTH, CPP product Cystatin C |
| Type V | Secondary Cardiorenal syndrome | Systemic condition causing both cardiac and kidney dysfunction | Diabetes mellitus, Sepsis | --- |

*ET-1 indicates endothelin-1;CPK-MB, creatine phosphokinase-MB; BNP, B-type natriuretic peptide; TNF, tumor-necrosis factor; IL, interleukin; PTH, parathyroid hormone; and CPP, calcium-phosphate product.

# THE CARDIO-RENAL CONNECTORS




Bongartz and colleagues recently proposed an extension to the Guytonian model of volume and blood pressure control called “the cardiorenal connection.” Actions of the regulators of Guyton’s model were coupled to their extended actions on structure and function of the heart and the kidney. Thus, it can be stated that “when one of the organs fails, a vicious circle develops in which the RAAS, the NO-ROS balance, the sympathetic nervous system, and inflammation interact and synergize, called the “cardiorenal connection”

## CARDIORENAL FAILURE

Renal impairment in patients with HF is increasingly recognized as an independent risk factor for morbidity and mortality [(14)]. In an analysis of patients enrolled in the CHARM study (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) Hillege et al. showed that the level of renal dysfunction was a potent independent predictor of death or HF admission [(15)].

The Acute Decompensated Heart Failure National Registry (ADHERE), a large database of 105,388 patients with HF requiring hospitalization in the United States, reported that 30% had an additional diagnosis consistent with chronic kidney disease[(16)]. Approximately 20% of patients had serum creatinine (Cr) >2.0 mg/dL, 9% had Creatinine >3.0 mg/dL, and 5% were receiving dialysis therapy.

Smith et al.[(17)] conducted a systematic review and meta-analysis of 16 studies characterizing the association between renal impairment and mortality in 80,098 hospitalized and nonhospitalized HF patients (1945 through May 2005). Renal impairment was defined variably as Cr >1.0 mg/dL, Cr clearance (CrCl) or estimated glomerular filtration rate (eGFR) <90 mL/min, or cystatin-C >1.03 mg/dL. Moderate to severe renal impairment was defined as Cr 1.5 mg/ dL, CrCl or eGFR <53 mL/min, or cystatin-C 1.56 mg/dL. A total of 63% of patients had any renal impairment, and 29% had moderate to severe impairment. Adjusted all-cause mortality was significantly increased for patients with any renal impairment. Mortality worsened incrementally across the range of renal function, with 15% increased risk for every 0.5 mg/dL increase in Cr and 7% increased risk for every 10 mL/min decrease in eGFR [(18)].

Owan et al. [(19)] recently reported on secular trends in the severity of renal dysfunction in

patients with ADHF in 6,440 consecutive unique patients hospitalized for HF therapy at Mayo Clinic Hospitals, Rochester, MN, from January1, 1987, to December 31, 2002. Over the 16-yr time period, age and admission Cr increased, eGFR decreased, and hemoglobin decreased. The more dominant role of renal dysfunction in HF was also stressed in the recent Evaluation Study of Congestive Heart Failure and pulmonary Artery Catheterization Effectiveness(ESCAPE) trial, where it was emphasized that episodes of HF decompensation were less commonly associated with uncorrected vasoconstriction and more commonly associated with renal dysfunction with requirement of higher diuretic doses at discharge than historically noted [20]. Thus, the severity of cardiorenal failure in patients hospitalized for HF is increasing. Importantly, cardiorenal failure is equally prevalent in patients with HF and normal ejection fraction (diastolic HF) or reduced ejection fraction (systolic HF) [18, 21]

**WORSENING RENAL FUNCTION**

Several studies have established that >70% of patients will experience some increase in Creatinine during hospitalization for HF, with approximately 20% to 30% of HF patients experiencing an increase of >0.3 mg/dL (19, 21). Worsening renal function occurs relatively early in the course of the hospitalization [22]. Any change in Cr has been shown to be associated with longer length of stay, increased costs, and increased short-term and long-term mortality. The association of worsening renal function with poorer outcomes is independent of the degree of baseline renal dysfunction and many other pertinent covariables [23, 24]. Nonetheless, it remains unclear whether the worsening renal function itself contributes to the increased mortality or whether it merely serves as a marker of more severe cardiac and/or renal dysfunction.

Importantly, worsening renal function is as common in diastolic HF as it is in systolic HF. While the severity of underlying renal dysfunction in ADHF patients has increased over time, Owan et al. [19] did not find any evidence of increases in the incidence of worsening renal function over time.

**DIURETIC RESISTANCE**

In patients with ADHF associated with volume overload, initial therapy focuses on sodium and fluid restriction and diuretics. Diuretic resistance has been defined as persistent pulmonary congestion with or without worsening renal function despite attempts at dieresis (Table 1).

The prevalence of diuretic resistance (DR) depends in part on the aggressiveness of the diuretic dosing. While worsening renal function commonly develops in the absence of persistent congestion when diuretic dosing has been too high (termed *overdiuresis*), worsening renal function also often occurs despite persistent pulmonary congestion in patients with diuretic resistance. Both DR and worsening renal function (WRF) are more common in patients with underlying renal dysfunction, and the triad of cardiorenal failure, DR, and worsening renal function despite marked persistent volume overload represents the most extreme manifestation of the cardiorenal syndrome.

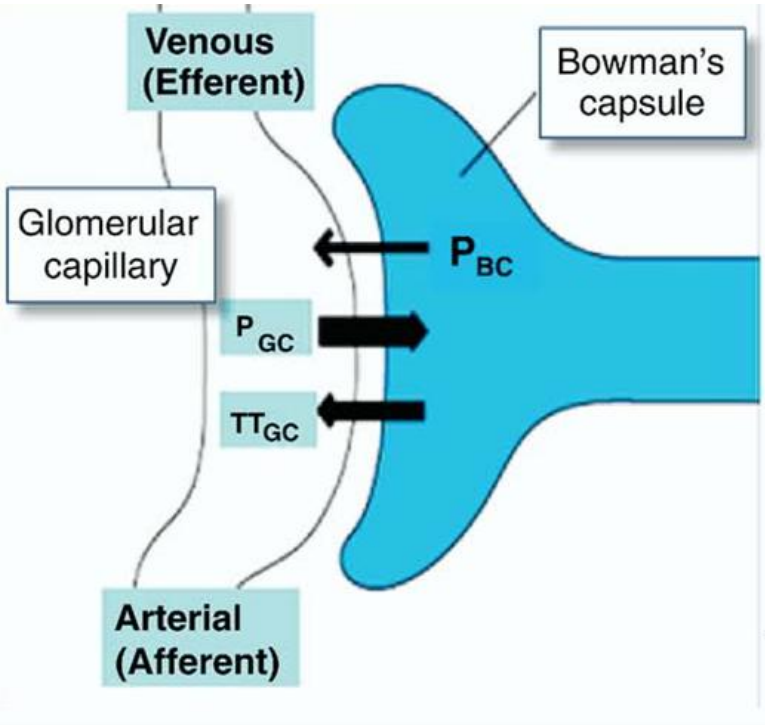
Two disparate analyses appeared in the Journal of American college of Cardiology in February 2009 issue: one evaluates hemodynamics associated with worsening renal function (WRF) in 145 patients hospitalized for acutely decompensated heart failure (ADHF)[25], and the other assesses the correlation between hemodynamics, renal function, and mortality in 2,557 patients undergoing right heart catheterization for various cardiovascular disorders [26]. Despite the

dissimilar patient populations, a strikingly similar message emerges: increased central venous pressure (CVP) is independently associated with renal dysfunction, WRF, and unfavorable outcomes. In the Dutch study, the detrimental effect of CVP on renal function and survival was greatest in those patients with preserved cardiac index (CI) [26].

The discordance between cardiac performance and renal function challenges the notion that, in heart failure (HF), renal insufficiency usually represents hypoperfusion of the kidney as the result of poor forward flow or overzealous diuresis. Instead, growing evidence shows that hypervolemia by itself is independently associated with mortality [27]. The authors of a study comparing blood volume measured by radiolabeled albumin with hemodynamics and outcomes in 43 nonedematous patients with HF demonstrated that 65% were hypervolemic [28]. Importantly, blood volume was closely correlated with pulmonary capillary wedge pressure (PCWP) and independently predicted 1-year risk of death or urgent cardiac transplantation, both significantly greater in the hypervolemic patients [28]. Observational data in patients with ADHF showed that pre-discharge reduction of PCWP <16 mm Hg, as opposed to an increased CI, predicted improved 2-year survival. Interestingly, in the Dutch study, increased CVP on admission, as well as insufficient reduction of CVP during hospitalization, were the strongest determinants for the development of WRF [25]. In contrast, impaired CI on admission and improvement in CI after intensive medical therapy had little effect on WRF. These intriguing observations raise questions about our current management strategy for acute HF, which has been to lower cardiac filling pressures while maintaining or enhancing CI [29]. What are the mechanisms by which venous congestion worsens renal function, and why is vigorous diuresis alone so often ineffective?

Normally, 85% of the total plasma volume resides in the venous circulation; only 15% is maintained in the arterial circuit. The primary regulation of renal sodium and water excretion and, thus, body fluid homeostasis, is modulated by the smaller arterial circulation, enabling the system responsible for the perfusion of the body's vital organs to respond to small changes in body fluid volume [30]. Heart failure results in a decrease in CI and a decrease in intra-arterial blood volume. Arterial hypovolemia inactivates the high pressure baroreceptors in the aortic arch and coronary sinus, attenuates the tonic inhibition of afferent parasympathetic signals to the central nervous system, and enhances sympathetic efferent tone, with subsequent activation of the renin-angiotensin-aldosterone system (RAAS) and non osmotic release of arginine-vasopressin (AVP)[30]. In the kidney, increased angiotensin II (Ang II) causes renal efferent arteriolar vasoconstriction, resulting in decreased renal blood flow (RBF) and increased filtration fraction. Together with renal nerve stimulation, the increased peritubular capillary oncotic pressure and reduced peritubular capillary hydrostatic pressure augment sodium reabsorption in the proximal tubule. Angiotensin II also directly stimulates proximal sodium reabsorption by activating sodium bicarbonate cotransporters and apical sodium-hydrogen exchangers. Finally, Ang II promotes aldosterone secretion, which boosts sodium reabsorption in the distal nephron [30]. Importantly, increased proximal sodium reabsorption decreases distal sodium and water delivery, stimulating macula densa cells to increase synthesis of renin that further amplifies neurohormonal activation [31]. Enhanced renal sodium and water reabsorption predominantly fills the compliant venous circulation, increasing CVP and atrial pressures. Normally, an increase in atrial pressure suppresses AVP release and enhances water diuresis, decreases renal sympathetic tone, and augments natriuretic peptide secretion. In patients with HF, these atrial–renal reflexes are overwhelmed by neurohormonal activation, evidenced by

# IMPACT OF VENOUS CONGESTION ON GLOMERULAR NET FILTRATION PRESSURE




| Forces | Normal: Afferent end of glomerular capillary (mmHg) | Normal: Efferent end of glomerular capillary (mmHg) | ↑ RA pressure: Afferent end of glomerular capillary (mmHg) | ↑ RA pressure: Efferent end of glomerular capillary (mmHg) |
|---|---|---|---|---|
| **1. Favoring Filtration** | | | | |
| Glomerular-capillary hydrostatic pressure, $P_{GC}$ | **60** | **58** | **55** | **63** |
| **2. Opposing Filtration** | | | | |
| a. Hydrostatic pressure in Bowman's capsule, $P_{BC}$ | **15** | **15** | **15** | **15** |
| b. Oncotic pressure in glomerular capillaries, $\pi_{GC}$ | **21** | **33** | **21** | **33** |
| **Net filtration pressure** (1-2) | **24** | **10** | **19** | **15** |
| *Filtration pressure:* | *14 mmHg* | | *4 mmHg* | |

persistent renal sodium and water retention despite elevated atrial pressures [30]. Transmission of venous congestion to the renal veins further impairs the glomerular filtration rate (GFR) (See Figure).

The authors of an isolated mammalian kidney study from 1931 showed that increased renal venous pressure was associated with reduced RBF, urine flow, and urinary sodium chloride excretion, abnormalities that were reversed by lowering renal venous pressure [32]. Years later, hypervolemia experimentally induced in dogs directly decreased GFR, independent of CI and RBF (33). A contemporary study in patients with ADHF revealed that an increased intra-abdominal pressure from ascites and visceral edema was correlated with the severity of renal dysfunction and that reduction of intra-abdominal pressure improved renal function [34]. Furthermore, in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, right atrial pressure emerged as the only hemodynamic variable correlated with baseline renal function, an independent predictor of mortality and HF hospitalization [35].

Despite these provocative data, it is premature to conclude that therapies specifically aimed at the reduction of CVP will actually reduce renal dysfunction or mortality in patients with HF. In the ESCAPE trial, therapy directed toward lowering measured PCWP and CVP produced no better outcomes than management aimed to reduce exam-based CVP [35]. Also unknown are the specific CVP values that must be achieved to improve renal function and outcomes. Perhaps the strategy to reduce filling pressures in HF remains appropriate, but our heavy reliance on the tactic of diuretics to achieve this goal may critically impact renal function and outcome. Loop

diuretics act in the thick, ascending limb of the loop of Henle, near the macula densa. Loop diuretics block sodium chloride uptake in the macula densa, independent of any effect on sodium and water balance, thereby stimulating the RAAS [36]. This pathophysiology, and the growing literature documenting the adverse consequences of diuretic use on ADHF outcomes [37], has lead to exploration of other approaches. If fluid removal by an alternative therapy, such as ultrafiltration, does not exceed the interstitial fluid mobilization rate of 14 to 15 ml/min, further activation of the RAAS is avoided. Moreover, for the same fluid volume, more sodium is removed by isotonic ultrafiltration than by diuretic-induced hypotonic diuresis [38]. Data from the UNLOAD (Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) trial on ADHF rehospitalization rates after ultrafiltration appear promising and await further confirmation in larger trials [39].

## RISK FACTORS FOR CARDIORENAL SYNDROME

The common risk factors of hypertension, diabetes mellitus, and atherosclerosis explain the high prevalence of coexistent cardiac and renal dysfunction. Success in preventing death from HF, acute myocardial infarction, stroke, and non cardiovascular disease may result in a longer exposure to risk factors for renal dysfunction contributing to more severe renal dysfunction in HF patients. Importantly, CrCl or eGFR as estimated by the simplified Modification of Diet in Renal Disease formula or Cockcroft-Gault formula is a better estimator of renal function than serum Cr, as serum Cr may overestimate renal function in the HF population, particularly in elderly women. On average, persons developing worsening renal function are older and have a greater prevalence of prior HF, renal dysfunction, diabetes, and hypertension.

## APPROACH TO THE CARDIORENAL SYNDROME

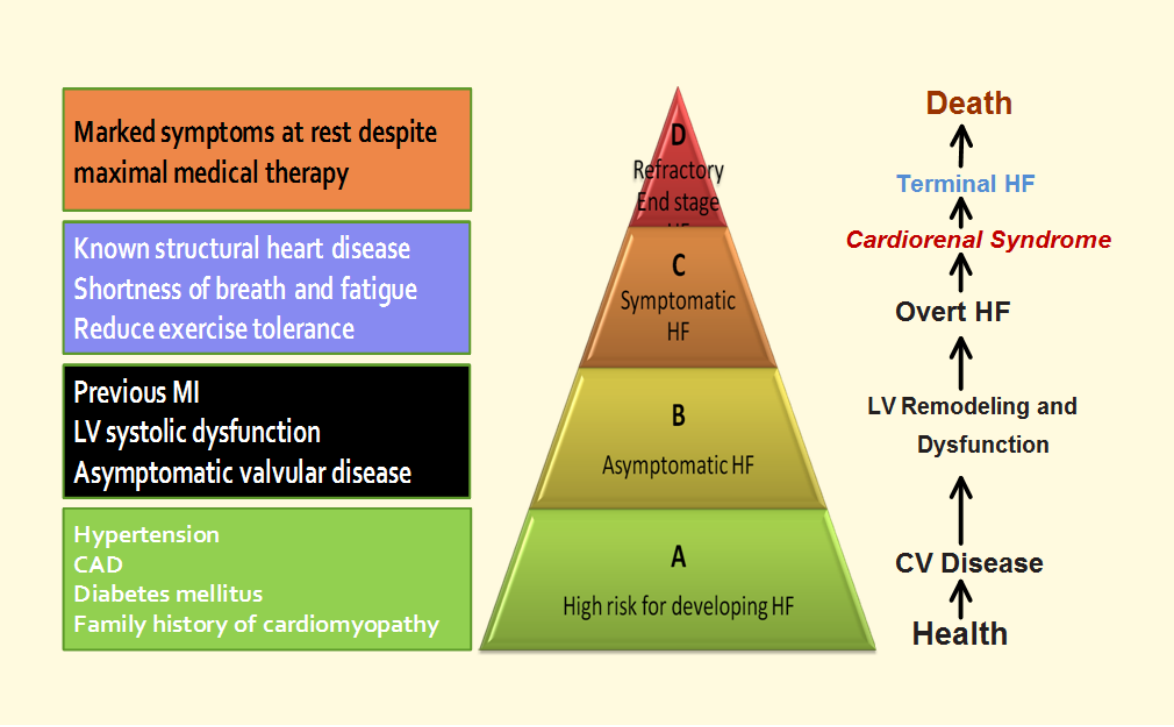
The development of worsening renal function and/or DR during the treatment of the patient with cardiorenal failure is a common and predictable but difficult clinical problem. There is no consistently effective strategy, and much of the approach is empirical.

| APPROACH TO THE CARDIORENAL SYNDROME | |
|---|---|
| 1 | Anticipate |
| 2 | Optimize Heart Failure therapy |
| 3 | Evaluate renal structure and function (ultrasonography accompanied by renal vascular evaluation with Doppler and resistive indices) |
| 4 | Optimize diuretic dosing |
| 5 | Consider renal-specific therapies<br>a. Renal-dose dopamine<br>b. Nesiritide<br>c. Ultrafiltration and/or hemodialysis |
| 6 | Investigational therapies<br>a. Hypertonic saline + high-dose loop diuretics<br>b. Vasopressin antagonists<br>c. Adenosine antagonists |

## RECOGNIZE THE CARDIORENAL SYNDROME AND ANTICIPATE THE DEVELOPMENT OF WORSENING RENAL FUNCTION

Patients developing the cardiorenal syndrome in the setting of ADHF and persistent congestion are usually those with long-standing HF who experience an episode of decompensation despite adequate chronic HF therapy and who are already on chronic high-dose diuretic therapy. A progressive increase in Cr over recent years is typically evident and reflects not only the

underlying renal disease but the additional effect of the HF state as outlined previously. Patients with severe diastolic dysfunction (regardless of ejection fraction), secondary pulmonary hypertension, right ventricular dysfunction, marked functional tricuspid or mitral regurgitation, previous HF hospitalizations, a history of worsening renal function with previous ADHF episodes, or a history of transient dialysis (often after cardiac surgery or contrast administration) are at the highest risk. In many patients, development of the cardiorenal syndrome is a marker of the transition to stage D HF (See Figure). It is helpful to address the potential for worsening renal function with the patient at admission, including the prognostic implications of cardiorenal syndrome and stage D. An assessment of suitability for dialysis and advanced HF therapies, such as cardiac support (left ventricular assist device) or replacement (transplantation), should be made.




**Development of the cardiorenal syndrome as a marker of the transition to stage D heart failure**

Unfortunately, the vast majority of patients developing cardiorenal syndrome will not be candidates for advanced HF treatments, such as transplantation or left ventricular assist device, due to age and comorbidities. Anticipation of a very high risk for cardiorenal syndrome may support use of different strategies, such as more gradual volume removal or early use of (potentially) renal-protective strategies (discussed subsequently). However, whether slower volume removal or the variety of strategies available to preserve renal function will affect the development of the cardiorenal syndrome or improve outcomes is unknown.

## OPTIMIZE HEART FAILURE THERAPY

While therapy for ADHF often focuses on volume removal, careful review of the patient's HF therapy addressing the adequacy of vasodilator therapy, blood pressure control, or the potential for additional adjuvant therapy (digoxin, nitrates, cardiac resynchronization therapy) is important. Addressing factors that can provide additional symptom relief (paracentesis, thoracentesis) or optimize cardiac function (revascularization, correction of valve disease) should be considered early in the hospitalization. Many centers are still aggressive in the use of pulmonary artery catheters in difficult patients with cardiorenal syndrome to ensure that hemodynamics and standard HF therapies are optimized. Importantly, pulmonary artery catheter guided therapy commonly includes administration of an inotropic agent. Use of inotropic agents is consistently associated with poorer outcomes, whether in randomized trials or retrospective registries, and their ability to improve cardiac status in the hospital must not be equated with improved outcomes [40, 41].

## EVALUATE RENAL STRUCTURE AND FUNCTION

A careful history should identify factors that may be exacerbating disease and HF related renal dysfunction, such as infection, use of nephrotoxic agents, or risk factors for renal artery stenosis. Urinalysis, including microscopic analysis for urine eosinophils (seen in allergic interstitial nephritis or renal atheroembolism), renal ultrasound with Doppler imaging of renal arteries, and assessment of renal resistive indices, should be performed to assess renal size, renal artery stenosis, or obstruction and to characterize structural renal disease. If suspicion for renal artery stenosis is high, one can consider magnetic resonance imaging with angiography, although this is increasingly difficult in patients with systolic HF due to the presence of devices. Computed tomography angiography to assess for renal artery stenosis is often precluded because of the potentially high risk of contrast nephrotoxicity and renal atheroembolism. The risk-benefit ratio of contrast administration must be weighed carefully as even gadolinium (used with magnetic resonance angiography) carries risk of worsening renal function in HF patients. The role of renal biopsy has not been well defined in this setting, and clearly the risk-benefit ratio must be considered on an individual basis. However, in patients in whom the cause of acute renal failure is unclear even after a thorough history, physical examination, and laboratory and clinical investigations are performed, renal biopsy may provide definitive diagnostic information that is helpful in guiding therapy or prognosis.

## OPTIMIZE DIURETIC DOSING

Continuous infusion of loop diuretics (i.e., furosemide) may provide greater diuresis and better

safety profile compared with bolus injection. A meta-analysis of studies comparing continuous infusion vs.bolus injection of loop diuretics in acutely decompensated HF was performed by Salvador et al [42], urine output was greater in patients given continuous infusion. Electrolyte disturbances (hypokalemia, hypomagnesemia) were not significantly different between the two groups. There were fewer adverse effects (tinnitus and hearing loss) after continuous infusion compared with bolus injection. In addition, one study showed that the hospital duration of stay was significantly shortened (by 3.1 days), one study showed lower cardiac mortality, and two studies showed lower all-cause mortality in patients treated with continuous infusion vs. bolus injection of furosemide. Therefore, most studies suggest a greater diuresis and better safety profile when loop diuretics are given as a continuous infusion. However evidence is insufficient to definitively recommend one method of administering loop diuretics, and further larger studies are needed.

In addition to the mode of administration of loop diuretics, the addition of thiazide diuretics in combination with loop diuretics has been shown to improve efficacy and diuretic responsiveness in severe refractory HF [43, 44]. Dormans and Gerlag [44] found that in 20 patients with New York Heart Association (NYHA) class III and IV HF, edema, and diuretic resistance, addition of hydrochlorothiazide to furosemide resulted in a mean body weight reduction of 6.7 $\pm$3.3 kg per patient. Mean daily urine volume increased and fractional sodium excretion increased significantly ($p < .001$ for both). Due to potentially dangerous adverse effects, such as hypokalemia, metabolic alkalosis, and dehydration, careful monitoring of the patient is necessary if combination diuretics are used.

## CONSIDER RENAL-SPECIFIC THERAPIES

### RENAL DOSE DOPAMINE:

The use of low-dose or "renal dose" dopamine, at doses <5 μg/kg/min has been proposed in the past to prevent or treat acute renal failure and to increase urine output in HF patients refractory to loop diuretics. Physiologically, low-dose dopamine increases renal blood flow and increases urine output by stimulating both dopaminergic (DA-1 and DA-2) and adrenergic (both α and β) receptors. Therefore, low-dose dopamine may affect renal blood flow by direct vasodilation (dopamine receptors), by increasing cardiac output (β receptors), or by increasing perfusion pressure via vasoconstriction (α receptors). At low doses (especially <2 μg/kg/min), dopaminergic receptor effects predominate, resulting in renal vasodilatation and increased renal blood flow. Dopamine also inhibits aldosterone release and inhibits sodium-potassium ATPase at the tubular epithelial cell level, resulting in increased sodium excretion and thereby diuresis [45 – 49]. Several early studies showed significantly increased natriuresis, diuresis, and improved renal function with use of low-dose dopamine [48, 50, 51]. Other studies have also suggested a role for dobutamine, ibopamine (a dopamine congener), and fenoldopam in reducing renal vascular resistance, increasing cardiac output, and increasing natriuresis, urine flow, and CrCl. However, these studies were largely small, underpowered, and nonrandomized.

The overwhelming consensus among studies with more rigorous methodology is that there is no convincing scientific evidence of a beneficial effect with low-dose dopamine beyond a possible natriuretic diuresis [52]. Furthermore, dopamine has significant potential side effects, including digital cyanosis and gangrene [53]. Kellum and Decker [45] concluded that "the use of low-dose dopamine for the treatment or prevention of acute renal failure cannot be justified

on the basis of available evidence and should be eliminated from routine clinical use." Therefore, based on these studies, there is little if any role for renal dose dopamine in heart failure therapy in attempts to preserve renal function.

**NESIRITIDE AS RENAL PROTECTIVE THERAPY:**

Nesiritide (synthetic human B-type natriuretic peptide) is a potent vasodilator that has been used to rapidly reduce cardiac filling pressures and improve dyspnoea in patients with ADHF [54-57]. Several early moderately sized controlled trials [57–61] suggested that nesiritide was safe in the short-term management of these patients. However, studies conflict on nesiritide's effects on renal function, natriuresis, and diuresis.

Recently, in a preliminary report from Owan et al. [62], use of standard dose nesiritide, despite lowering blood pressure, was associated with improved renal function indices at 24 hours. Furthermore, preliminary findings from a trial in which nesiritide was administered at a standard dose (0.01 μg/kg/min) without a bolus to patients undergoing cardiac surgery have been reported, and a marked reduction in the incidence of renal dysfunction was noted[63]. Thus, the role of nesiritide as a renal-protective and diuresis-promoting therapy in ADHF remains promising but requires further study.

**ULTRAFILTRATION:**

When traditional medical therapies fail or patients become resistant to diuretics, other therapeutic options must be undertaken to relieve volume overload. Ultrafiltration has been recognized as a

viable treatment option by the Heart Failure Society of America and the ACC/AHA for diuretic-resistant HF (strength of evidence = C) [64].

Ultrafiltration (UF) or slow continuous UF filters plasma water directly across a semipermeable membrane in response to a transmembrane pressure gradient, resulting in an ultrafiltrate that is isoosmotic compared with plasma water [65, 66]. In contrast, hemodialysis involves the passage of solutes and water from the blood across a semipermeable membrane down a concentration gradient between the blood and dialysate via diffusion, allowing for changes in electrolytes and small solutes. Hemofiltration uses membranes with greatly increased hydraulic permeability, so that solute is removed by bulk flow [66, 67]. In continuous venovenous hemofiltration, fluid and medium-sized solutes are removed by bulk flow and solvent drag at large volumes per hour, with replacement fluids administered to the patient simultaneously. This allows for clearance of potentially toxic solutes, while maintaining stable hemodynamics. Continuous veno-venous hemodiafiltration is essentially continuous venovenous hemofiltration with the addition of dialysate on the other side of the semipermeable membrane, allowing diffusion of small solutes to occur simultaneously with continuous veno-venous hemofiltration.

Ultrafiltration has been studied extensively and proven to be an effective treatment for patients with HF who are fluid overloaded and diuretic resistant, with fewer adverse effects than hemodialysis and peritoneal dialysis. UF promotes the resorption of systemic extravascular water and can effectively treat pulmonary edema in patients with HF.

The radiographic score of lung water, exercise tolerance (peak oxygen consumption), dynamic lung compliance, ventilation, tidal volume, and deadspace/ tidal volume ratio at peak exercise

improved significantly [68]. In addition, there were improvements in neurohumoral responses [69]. In contrast, furosemide infusion at a dosage that achieved equivalent fluid removal produced clearing of the lungs, but this benefit was not sustained, and the dramatic improvements in lung function, exercise performance, and neurohumoral function observed with the UF treatment were not observed with diuretic administration titrated to produce a similar reduction in right atrial pressure[69, 70]. These remarkable observations suggest that this form of therapy may have unique benefits, but these elegant studies have not been repeated in patients with ADHF and marked volume overload.

Recently, a peripherally inserted UF device manufactured by HF Solutions (Aquadex, System 100) was approved by the FDA for therapy in HF. This device allows UF to be performed at very low flows (40 mL/min) using only a peripheral intravenous catheter and a midline catheter in an antecubital vein, with only 33– 40 mL of extracorporeal blood at any given time. This simple machine is designed for use by non nephrologists and nurses, avoiding the need for intensive care or dialysis units.

Importantly, UF was shown to remove more sodium and less potassium than diuretics for an equivalent amount of volume reduction [71]. This critical difference may promote more sustained volume reduction and offer the potential for improved long-term outcomes with UF compared with diuretics. However, the expense and complexity of treatment limit the potential use of UF as a first-line strategy in all patients with ADHF. Whether rescue therapy with UF in patients with established cardiorenal syndrome will prove superior to standard care remains to be established.

## INVESTIGATIONAL THERAPIES FOR CARDIORENAL SYNDROME

### HYPERTONIC SALINE PLUS FUROSEMIDE:

Paterna et al [72] described success in treating patients with refractory HF with the combination of high-dose furosemide and small-volume hypertonic saline solution. A total of 94 patients with refractory HF were randomized to receive either high-dose intravenous furosemide (500 – 1000 mg) plus hypertonic saline solution twice a day in 30 mins or intravenous bolus furosemide (500 –1000 mg) twice a day, for 4–6 days. Significant increases in daily diuresis and natriuresis, as well as improvements in B-type natriuretic peptide and bioelectrical impedance measurements, were observed in the furosemide plus hypertonic saline solution group. The hypertonic saline solution group also showed a significant reduction in hospitalization time and readmission rate.

Potential mechanisms of increased sodium load in the therapy of HF may relate to an acute osmotic effect of hypertonic saline to increase mobilization of extravascular fluid into the central circulation and renal circulation. Increases in renal blood flow may facilitate diuretic responsiveness. In addition, direct intra tubular effects of sodium flooding may overwhelm the rebound sodium retention seen in diuretic therapy, thus reducing the "braking phenomenon" discussed previously. Furthermore, neurohormone levels may have been suppressed by hypertonic saline. The increased intravascular volume and greater distal tubule sodium delivery may inhibit the RAAS, causing reductions in aldosterone, angiotensin II, and vasopressin (or antidiuretic hormone) release despite a temporary increase in serum osmolarity. There may also be a small contribution of increased intravascular volume causing inhibition of ADH release via volume/ baroreceptors, leading to reduced free water resorption via aquaporin

channels in the collecting tubules of the kidney [74]. This novel strategy has yet to be tested by other groups.

## VASOPRESSIN ANTAGONISTS IN HEART FAILURE THERAPY:

Vasopressin antagonists represent another promising class of therapeutics that may improve aquaresis and hyponatremia in patients with chronic HF. Vasopressin, also known as arginine vasopressin or antidiuretic hormone, is a cyclic hexapeptide produced in the hypothalamus and released from secretory granules in the posterior pituitary lobe in response to hyperosmolality, volume depletion, angiotensin II, and sympathetic stimulation.

Vasopressin causes vasoconstriction and renal water resorption via the vasopressin receptor subtypes V1a (vascular), V2 (renal), and V3 (pituitary) receptors [75, 76]. V1a receptors, found in vascular smooth muscle cells and the kidney, mediate vasoconstriction and prostaglandin production at supra-physiologic concentrations of vasopressin [77]. V2 receptors, found in the renal collecting tubules (principal cells), mediate renal water resorption via insertion of aquaporin 2 channels into the luminal membranes and also release of von Willebrand factor and factor VIII from the vascular endothelium. V3 receptors, found in the pituitary gland, are responsible for stimulating adrenocorticotropic hormone secretion by pituitary corticotropes.

In HF, vasopressin levels are elevated due to signaling of the carotid sinus baroreceptors functioning as volume receptors in the setting of decreased effective arterial blood volume from low cardiac output. When systemic blood pressure drops sufficiently, as in advanced HF, antidiuretic hormone secretion markedly increases to levels that far exceed those induced

by changes in plasma osmolality. In addition, the volume depletion can prevent the inhibition of antidiuretic hormone release normally induced by a decrease in plasma osmolality, which contributes to the development of hyponatremia in HF.

Antagonism of the V1a and V2 receptors may be beneficial in HF patients [77–80]. Antagonism of V1a receptors increases cardiac output, reduces total peripheral vascular resistance, reduces mean arterial blood pressure, and inhibits vasopressin-mediated cardiomyocyte hypertrophy [77]. Antagonism of V2 receptors results in aquaresis, causing increased serum sodium concentration and reduced cardiac preload [77]. In HF, two vasopressin antagonists have shown promise in early clinical trials:

1) conivaptan (YM-087), an oral or intravenous V1a/V2-receptor antagonist; and
2) tolvaptan (OPC-41061), an oral specific V2-receptor antagonist.

Conivaptan reduced preload and increased urine output and serum sodium levels. Currently only the intravenous formulation of conivaptan has been developed and approved and it is only approved for treatment of patients with euvolemic hyponatremia.

Tolvaptan, an oral V2-receptor antagonist, has been shown to induce aquaresis in humans[81, 82]. Tolvaptan significantly decreased body weight, increased urine volume, increased net fluid loss, decreased urine osmolality, increased mean total 24-hr urinary sodium excretion, increased serum sodium, and improved edema when combined with standard diuretic regime. Its effect was observed primarily on the first day. After 24 hrs, patients treated with tolvaptan had a significant reduction in body weight compared with those administered placebo; this effect was not dose dependent.

The efficacy of Vasopressin Antagonism in heart failure Study with Tolvaptan (EVEREST) trial is an ongoing international, multicenter study designed to evaluate the long-term efficacy and safety of oral once-daily tolvaptan in patients hospitalized with worsening HF[83].

**ADENOSINE ANTAGONISTS IN HEART FAILURE THERAPY:**

Another promising new class of therapeutic agents is the A1 adenosine receptor antagonists. Plasma adenosine levels are elevated in patients with HF, with increasing levels as the severity of disease increases [83]. TGF promotes release of adenosine, and adenosine binding to A1 receptors causes vasoconstriction of the afferent arteriole, decreased renal blood flow and GFR, and enhanced sodium resorption by the proximal tubule. Antagonism of A1 adenosine receptors has the potential to improve renal function and overcome DR in patients with HF by disrupting the TGF loop [84].

# MATERIALS AND METHODS

# MATERIALS AND METHODS OF THE STUDY

## PATIENT SELECTION

The study group comprised of 50 heart failure patients. The patient subgroup was drawn from a consecutive series of 78 heart failure patients admitted in the Department of Medicine, Stanley Medical College and Government Stanley hospital, during the period of 4 months from March 1st 2010 to June 30th 2010.

For the study purpose clinical diagnosis of heart failure was confirmed with echocardiographic evaluation.

## INCLUSION CRITERIA

All patients admitted with cardiac failure of any etiology with a duration of hospital stay more than 24 hrs with or without cardiorenal dysfunction.

## EXCLUSION CRITERIA

1. Patients with documented chronic kidney disease including renal artery stenosis.
2. Patients with Diabetic nephropathy (proteinuria >300mg/24 hrs).
3. Patients with history of NSAID abuse.
4. Serum creatinine >5 mg/dL
5. Patients not satisfying above criteria( hospital stay <24 hrs)

## PATIENT EVALUATION

Patients included in the study were thoroughly evaluated clinically, biochemically, ultrasonographically and echocardiographically.

Patients name, age, sex, marital and socioeconomic status were noted as part of positive data. Presenting complaints of breathlessness on exertion(NYHA class), pedal edema, abdominal distension, chest pain, palpitation and fatigue were analyzed in detail, evidence of coronary artery disease, rheumatic heart disease, hypertension, diabetes mellitus, dyslipidemia, sedentary life style, obesity, current active smoking, current alcohol abuse and family history of risk factors including cardiomyopathy were obtained.

A clinical examination pertaining to heart failure was performed including a relevant general examination, vital signs and cardiovascular system. Other systems of respiratory, gastrointestinal and nervous system were examined and relevant details were noted.

The clinical diagnosis of heart failure was made based on ACC/AHA guidelines consisting of the pyramid approach to heart failure stages. Obesity was defined based on BMI, dyslipidemia on serum total cholesterol, smoking by Smoking Index and alcohol use >100ml/day for > 3 months.

Biochemical investigations done in this study included admission blood glucose, fasting and post prandial blood glucose, admission blood urea and serum creatinine, myocardial enzyme assay for acute coronary syndromes, fasting lipid profile, thyroid function test and repeat serum creatinine periodically (24 hrs, 48 hrs and on discharge). Chest roentgenogram PA view and ultrasonogram were also done.

Patients with active urinary sediments on microscopic examination were excluded from study. 24 hours Urine protein was obtained from each of these patients and those patients with proteinuria more than 300mg/24 hrs were also excluded from the study.

Creatinine clearance was estimated using Cockroft- Gault formula.

Echocardiography was done for all these patients. Both 2D and color Doppler echocardiography was done by a single experienced cardiologist. Left ventricular systolic performance was quantified as the LV ejection fraction. The operational definition of systolic dysfunction for study purpose is an ejection fraction of less than 50%. The left ventricular diastolic performance was quantified by Doppler and graded from I to III.

All clinical biochemical and echocardiographic variables were duly entered in a proforma especially designed for the study.

**PATIENT FOLLOW UP**

All the 50 patients included in the study were followed up till the time of discharge, and were followed for a minimum period of 2 months. All details regarding functional improvement, worsening symptoms, duration of hospital stay and in hospital death were carefully recorded. Information about deceased patients were obtained from family members. Particular attention was given to the circumstances of each death.

**STUDY DESIGN**

This study is a prospective cross sectional observational study.

# OBSERVATIONS AND

# STATISTICAL ANALYSIS

# OBSERVATIONS AND STATISTICAL ANALYSIS

The study population was subgrouped into heart failure alone group and heart failure with cardiorenal syndrome (CRS) group (defined by serum creatinine ≥ 1.4 mg/dL or creatinine clearance <60 ml/min or rise in serum creatinine >25% (>0.3 mg/dL) of baseline on attempted diuresis).

## STATISTICAL METHODS

All continuous variables were assumed to be normally distributed and are reported as arithmetic mean with their standard deviation. The 95% confidence intervals are also reported where clinically applicable. The Fisher's Exact test was used to compare and analyze the data. The null hypothesis was rejected at the 95% confidence interval, considering a probability value of $P < 0.05$ as statistically significant.

Statistical analysis was done using IBM SPSS® Statistics Version 19.

# RESULTS

# RESULTS

50 patients who were admitted in medical wards with heart failure who satisfied the inclusion and exclusion criteria were enrolled in this study. Out of the 50 patients, 32 were males and 18 were females. The youngest among them was 16 yrs and oldest being 72 years of age.

**TABLE -1**

**SEXWISE DISTRIBUTION OF PATIENTS IN THE STUDY**

| SEX | NUMBER OF PATIENTS | PERCENTAGE |
|---|---|---|
| **MALES** | **32** | **64%** |
| **FEMALES** | **18** | **36%** |

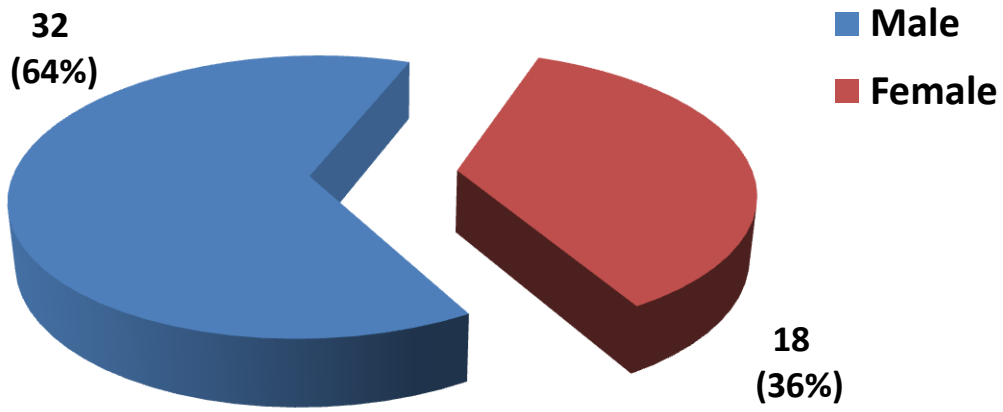
18 patients out of 50 satisfied criteria for diagnosis of heart failure with Cardiorenal Syndrome (Serum creatinine >1.3 mg% at admission and creatinine clearance <60 ml/kg/1.73m² OR a rise in serum creatinine >25% on attempted diuresis). Further analysis were carried out among this subgroup labeling them as CRS group and the remaining 32 patients as Heart Failure Alone group.

**TABLE – 2 SEXWISE DISTRIBUTION OF PATIENTS IN THE STUDY GROUPS**

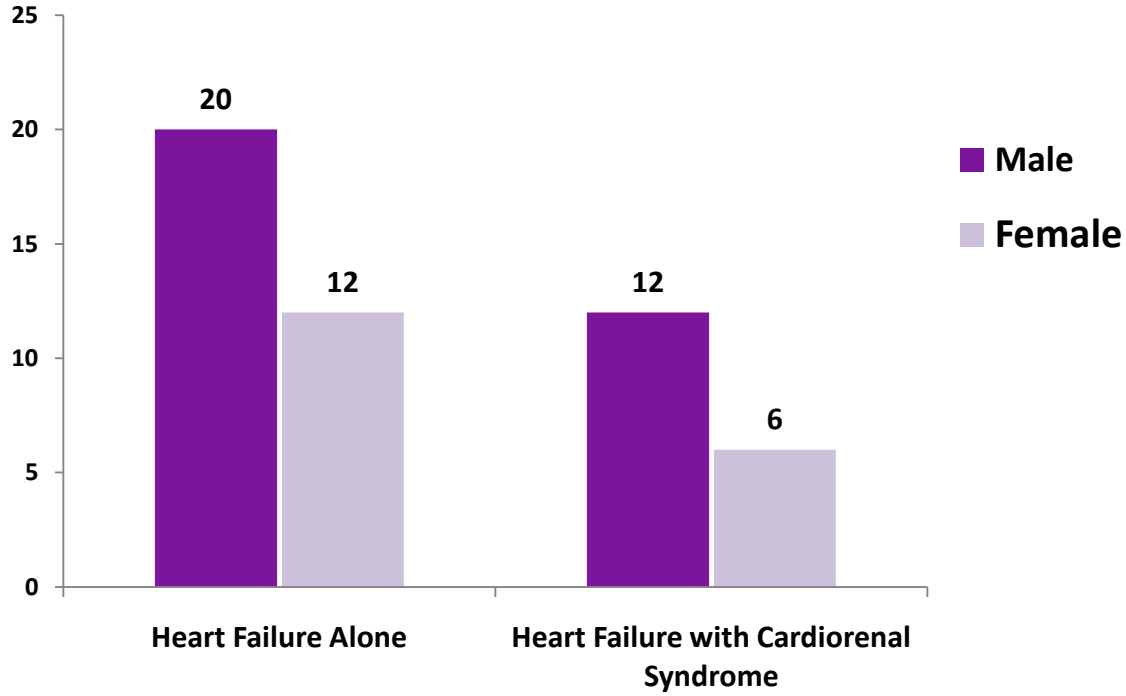
| **HEART FAILURE ALONE** | | |
|---|---|---|
| **MALE** | 20 | 62.5% |
| **FEMALE** | 12 | 37.5% |
| **TOTAL** | 32 | 100% |

| **CARDIORENAL SYNDROME** | | |
|---|---|---|
| **MALE** | 12 | 66.66% |
| **FEMALE** | 6 | 33.33% |
| **TOTAL** | 18 | 100% |

## Sex Distribution in Study Population




## Sex Distribution in Study Groups



## ETIOLOGY OF HEART FAILURE

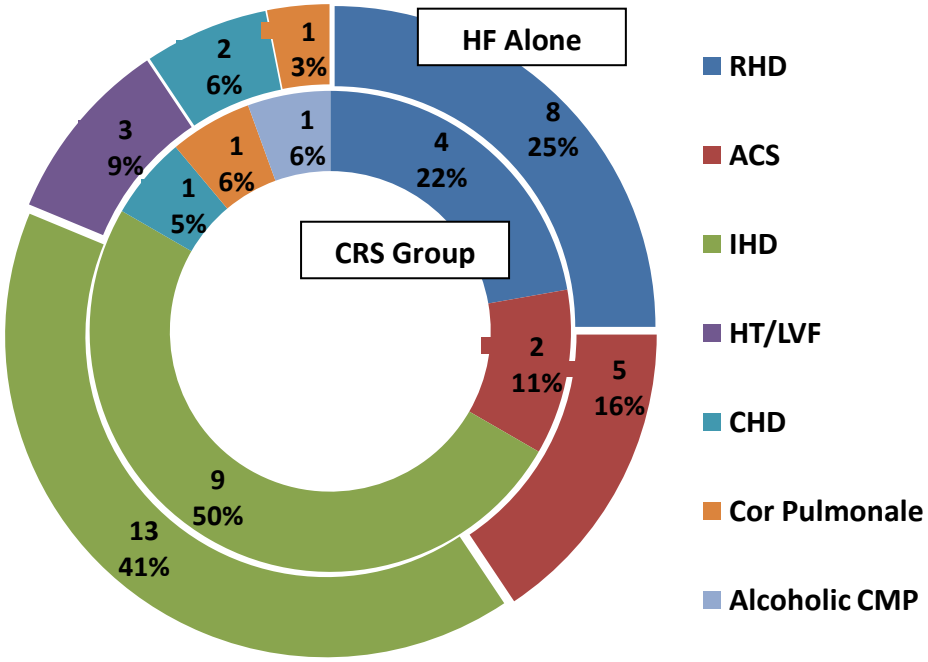
Both groups were comparable as far as the etiology of heart failure was concerned. Half of the patients were ischemic heart disease and another one-fourth were having rheumatic heart disease in both groups.

**TABLE – 3**

**ETIOLOGY OF HEART FAILURE**

| ETIOLOGY | HEART FAILURE ALONE | CRS GROUP |
|---|---|---|
| **RHD** | 8 | 4 |
| **ACS** | 5 | 2 |
| **IHD** | 13 | 9 |
| **HT/LVF** | 3 | 0 |
| **Congenital Heart Disease** | 2 | 1 |
| **Cor Pulmonale** | 1 | 1 |
| **Alcoholic Cardiomyopathy** | 0 | 1 |
| **Total** | **32** | **18** |

## ETIOLOGY OF HEART FAILURE




## AGE WISE DISTRIBUTION OF PATIENTS IN STUDY GROUP

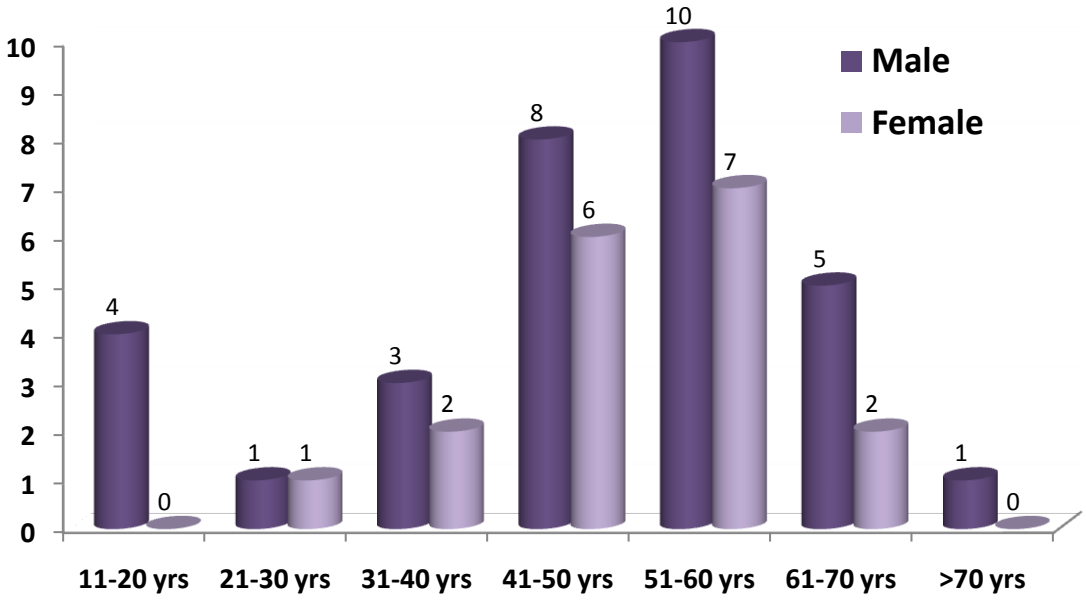


**TABLE - 4**

**AGE WISE DISTRIBUTION OF PATIENTS IN STUDY GROUP**

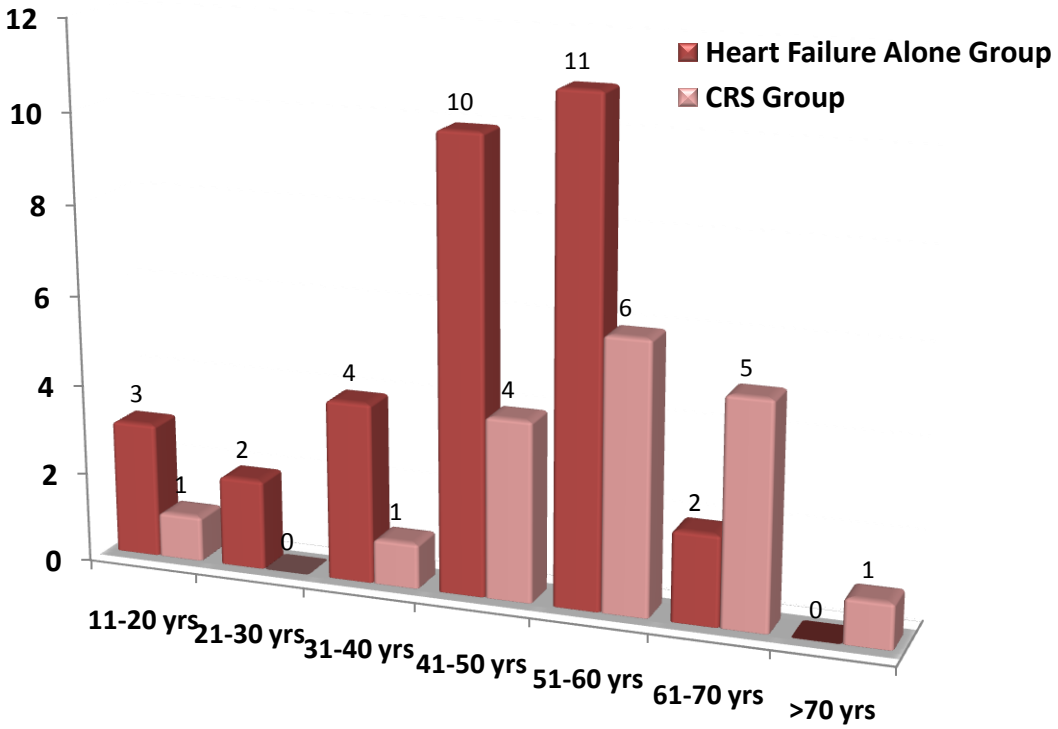
| Age Group | Male | Female | Total |
|---|---|---|---|
| **11-20 years** | 4 | 0 | 4 |
| **21-30 years** | 1 | 1 | 2 |
| **31-40 years** | 3 | 2 | 5 |
| **41-50 years** | 8 | 6 | 14 |
| **51-60 years** | 10 | 7 | 17 |
| **61-70 years** | 5 | 2 | 7 |
| **71-80 years** | 1 | 0 | 1 |

**FREQUENCY DISTRIBUTION ACCORDING TO AGE GROUPS**

When the frequency distribution of two groups were plotted against age group intervals the CRS group had a skewing towards 50-70 years (negative skewing) and Heart failure alone group positively skewed in 40-60 yrs (see chart next page).

Median age of CRS group is 58 years (Minimum 16 yrs and maximum 72 yrs) and that of heart failure alone group 48 yrs(Minimum 16 yrs and maximum 65 yrs), a difference of 10 years with a two-tailed p value of 0.0140, considered statistically significant.

## FREQUENCY DISTRIBUTION ACCORDING TO AGE GROUPS




Out of 50 patients majority belonged to NYHA Class III and Class IV (24 in each group, 96%), only 4 % patients were admitted with NYHA Class II symptoms.

The BMI of both groups were identical ( Mean BMI of heart failure alone group 22.97 kg/m² and that of cardiorenal syndrome group 23.33 kg/m² and the difference was statistically not significant (*p* value 0.6896).

## ANALYSIS OF RISK FACTORS

Univariate analysis of risk factors for the development cardiorenal syndrome in heart failure by Fisher's Exact Test using 2x2 contingency tables showed statistically significant risk associated with Diabetes Mellitus ( p=0.0176), Smoking (p=0.0352), and Left ventricular Diastolic dysfunction (p<0.0001, extremely significant). See Table – 5 & 6.

However Systemic Hypertension, Dyslipidemia, Alcoholism and Systolic left ventricular dysfunction (Ejection fraction <50%) failed to show any statistically significant difference. See table 5

## SERUM CRETININE AND CREATININE CLEARANCE

Mean serum creatinine at the time of admission in the heart failure alone group is 0.78 mg% (with 95% CI between 0.70-0.84) where as in the CRS group it is 1.91 mg% (with 95% CI between 1.52-2.30). The two-tailed *P* value is < 0.0001, considered extremely significant.

Similar was the results with creatinine clearance, mean in HF group of 100.81 (CI 90-111) and 40.01 in CRS group (CI 32.54-47.48), with *p* <0.0001.

**TABLE – 5**

**ANALYSIS OF RISK FACTORS**

| RISK FACTOR | | CRS | HF ALONE | *P* Value (Fisher's Exact Test) | Relative Risk |
|---|---|---|---|---|---|
| **Diabetes Mellitus** | Present | 13 | 11 | **0.0176** | **2.81** |
| | Absent | 5 | 21 | | |
| **Hypertension** | Present | 12 | 15 | 0.2410 | Not significant |
| | Absent | 6 | 17 | | |
| **Dyslipidemia** | Present | 11 | 18 | 0.7742 | Not significant |
| | Absent | 7 | 14 | | |
| **Smoking** | Present | 11 | 9 | **0.0352** | **2.36** |
| | Absent | 7 | 23 | | |
| **Alcoholism** | Present | 9 | 14 | 0.7709 | Not significant |
| | Absent | 9 | 18 | | |
| **Systolic Dysfunction** | Present | 11 | 14 | 0.3772 | Not significant |
| | Absent | 7 | 18 | | |
| **Diastolic Dysfunction** | Present | 17 | 12 | **<0.0001** | **12.310** |
| | Absent | 1 | 20 | | |

**TABLE – 6**

**ANALYSIS OF RISK FACTORS**

| **Parameter** | | **Heart Failure** | **CRS Group** | ***P* value** |
|---|---|---|---|---|
| Blood Sugar | Mean | 114.34 | 104.77 | 0.438 |
| | Standard Deviation | 47.583 | 27.32 | |
| | 95% CI | 97.19 -131.50 | 91.19 – 118.37 | |
| Total cholesterol | Mean | 208.44 | 211.22 | 0.789 |
| | Standard Deviation | 45.67 | 46.04 | |
| | 95% CI | 191.97 -224.91 | 198.12 -224.32 | |
| Cardiothoracic Ratio | Mean | 0.559 | 0.560 | 0.904 |
| | Standard Deviation | 0.033 | 0.035 | |
| | 95% CI | 0.55 – 0.57 | 0.55 -0.57 | |
| **Ejection fraction** | Mean | 50.81% | 41.17% | 0.0001 (**significant**) |
| | Standard Deviation | 6.30 | 10.08 | |
| | 95% CI | 48.54 – 53.08 | 36.15 - 46.18 | |

TABLE – 7

## SERUM CREATININE AND CREATININE CLEARANCE

### SERUM CREATININE ON ADMISSION

| Study Group | Sample size | Mean | Standard Deviation | Maximum | Minimum | T value | P value |
|---|---|---|---|---|---|---|---|
| Heart failure Alone | 32 | 0.78 | 0.19 | 1.2 | 0.6 | 7.839 | <0.0001 |
| Cardiorenal syndrome | 18 | 1.91 | 0.78 | 4.2 | 1.4 | | |

### CREATININE CLEARANCE ON ADMISSION

| Study Group | Sample size | Mean | Standard Deviation | Maximum | Minimum | T value | P value |
|---|---|---|---|---|---|---|---|
| Heart failure Alone | 32 | 100.82 | 28.52 | 202.0 | 63.20 | 8.388 | <0.0001 |
| Cardiorenal syndrome | 18 | 40.01 | 15.02 | 58.10 | 12.30 | | |

Thyroid function tests revealed 2 hypothyroid patients from the CRS group and one from heart failure alone group.

## MORBIDITY AND MORTALITY

Morbidity was assessed quantitatively in terms of duration of hospital stay in addition to the functional improvement. The mean duration of hospital stay was 6.78 days in heart failure group compared to 11.06 days for CRS group, the average difference of 3.28 days ($p<0.000$, statistically significant).

3 out of 18 CRS patients died before discharge( In hospital mortality of 16.66 %) whereas only 2 out of 32 in the heart failure alone group died within hospital( mortality 6.25%). 11 of the 18 CRS group patients had further renal impairment within 24 hrs of initiating diuretic therapy (61%).

CRS group had a prolonged hospital stay of 3.28 days as compared to heart failure alone group.

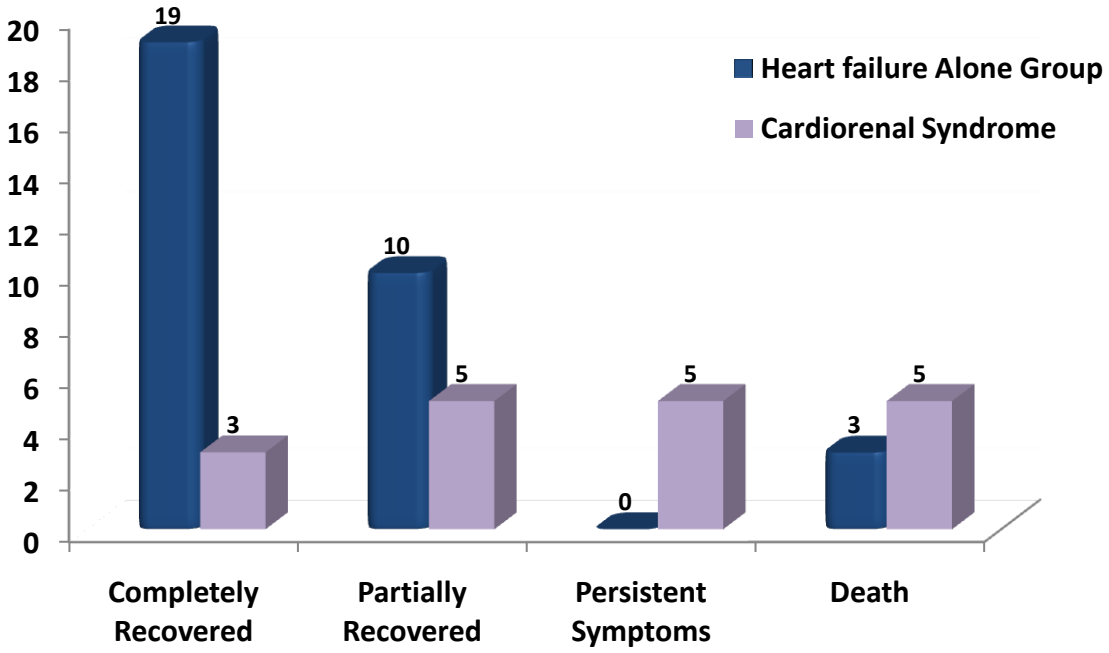
## FOLLOW UP AND OUTCOME

28% of CRS group patients(5 out of 18) died during hospital stay or within the 2 months follow up( 3 in-hospital, 2 during follow up ) considerably high as against 9.38% in Heart Failure alone group, approximately 3 fold increased mortality.

Only 16% completely recovered in CRS group as against 60% in others, 54% had persistent symptoms or improved only partially.

| OUTCOME | Group | |
|---|---|---|
| | CRS | HF Alone |
| Complete Recovery | 3 | 19 |
| Partial Recovery | 5 | 10 |
| Persistent Symptoms | 5 | 0 |
| **Death** | **5** | **3** |
| Total | 18 | 32 |

## Comparison of OUTCOME



# DISCUSSION

# DISCUSSION

In ambulatory heart failure patients, the presence of concomitant renal dysfunction is consistently a strong risk factor for morbidity and mortality. This risk becomes evident even at serum creatinine levels ≥1.4 mg/dL and estimated creatinine clearance values ≤60 mL/min. Furthermore, renal function is at least as powerful an adverse prognostic factor as most clinical variables, including ejection fraction and New York Heart Association functional class. Although renal dysfunction predicts all-cause mortality, it is most predictive of death from progressive heart failure, which suggests that it is a manifestation of and/or exacerbating factor for left ventricular dysfunction.

This study conducted at Stanley Medical College reaffirms the progressive nature of cardiorenal syndrome and its adverse outcome even in a small number of subjects. The studied population had a prevalence of 36% of Cardiorenal Syndrome in acute and chronic heart failure which is considered comparable to other studies. The prime focus of the study was in looking at the disease from functional aspect of the heart (i.e. Type I and Type II CRS). The more recent updates from across the world has a broader outlook and focuses Reno-Cardiac dysfunction also.

An attempt was made at assessing the predictors of morbidity and mortality, and Diabetes, Advancing age, 2 or more previous hospitalizations, a history of cardiorenal dysfunction, diastolic dysfunction, and a smoking index of >20 were independently associated and the association was extremely significant.

Surprisingly a history of hypertension could not predict cardiorenal syndrome by itself, likely to be due to the “Iceberg phenomenon” of non communicable disease. The fact that more than 90% of them had diastolic dysfunction of some degree during echo evaluation points the same. This

again throws light towards heightened pulmonary capillary wedge pressure (PCWP) and systemic venous congestion recently proposed as contributors for renal dysfunction in heart failure.

In the setting of hospitalization for decompensated heart failure, worsening renal function is even more important than baseline renal function for predicting adverse outcomes. This needs more randomized controlled trials and evaluation because an early identification of susceptible patient may benefit goal directed therapy.

Unfortunately, we have no evidence from clinical heart failure trials on which to base our therapy for patients with significant renal dysfunction, largely because these studies predominantly recruited populations with relatively preserved renal function. As a result, treatment is largely empirical. Inhibitors of the renin-angiotensin-aldosterone system are the cornerstone of our management of patients with left ventricular systolic dysfunction, and they also prevent progressive renal dysfunction in diabetic nephropathy and other forms of chronic kidney disease. Unfortunately, in the presence of underlying renal disease, use of angiotensin-converting enzyme (ACE) inhibitors and other renin-angiotensin-aldosterone inhibitors may be associated with elevations in creatinine, thereby creating a therapeutic dilemma. Although physicians frequently avoid or discontinue these medications for fear of exacerbating renal function, the rise in creatinine levels after the initiation of an ACE inhibitor actually may identify a subgroup of patients who will achieve the greatest benefit from their use. Furthermore, discontinuation of ACE inhibitors because of renal dysfunction identified a patient group with a high mortality risk during recent trials. Therefore, a sensible approach is to continue these agents despite a rise in creatinine, as long as renal dysfunction does not steadily deteriorate and severe hyperkalemia does not develop. Consider the diagnosis of renal artery stenosis in patients who are extremely

intolerant to ACE inhibitors. In patients who present with the combination of worsening renal function, volume overload, and diuretic refractoriness, the management of cardiorenal dysfunction is extremely challenging.

In short the study was valuable in identifying a subgroup of people among heart failure patients who had independent predictors of clinical deterioration, worsening renal function, increased morbidity and mortality who need special and intensive care and treatment strategies.

## STUDY LIMITATIONS

This study results are limited by a number of important factors. First and foremost is the sample size. For a disease which has a very high prevalence, it may be essentially difficult to draw conclusions from a small group of population especially considering the nature of the study centre (tertiary care). Population behavior is to seek health care only when the functional limitation becomes severe enough to disturb day to day activities. So the estimated prevalence may be an exaggerated one.

Second factor is the definition of cardiorenal syndrome. Several of the recent studies have accepted the criteria used in our study. There are difference of opinion in defining worsening renal function based on serum creatinine (Cr≥1.4 mg/dL OR Cr≥ 1.3 mg/dL, and also rise in creatinine on attempted diuresis, ≥0.3 mg% or >0.3 mg%) and may influence the prevalence.

The study patients received treatment from different physicians and the treatment protocol was individualized. So the outcome difference would have had some impact due to these factors.

The study was aimed mainly at looking the renal dysfunction secondary to heart failure (type 1 and type 2), the recent concept of cardiorenal syndrome has a broader view including Reno-cardiac syndromes. So the study underestimated the prevalence and actual prevalence may rise even to 50% or more.

# CONCLUSION

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The cardiorenal syndrome often heralds the transition of heart failure to an end-stage, preterminal (stage D) heart failure.

The conclusions of the study are the following.

1. The prevalence of Cardiorenal syndrome in heart failure is quite high (36%).
2. History of 2 or more previous hospitalizations and advancing age in patients with heart failure predispose them in developing cardiorenal syndrome. Patients who developed cardiorenal syndrome were older by a mean of 10 years (*p* value = 0.0140).
3. The relative risk of cardiorenal dysfunction is high with Smoking, Diabetes Mellitus and Left ventricular Diastolic Dysfunction.
4. In addition to prolonged hospitalization (by 3.28 days) and slower recovery, the development of cardiorenal syndrome is an independent predictor of frequent readmissions. The in-hospital and 2 month follow up mortality is 3 times higher in cardiorenal syndrome when compared to heart failure alone group.

Under-treatment of the cardiorenal syndrome may have lethal consequences at an individual level and huge potential adverse consequences at a public health level. The depth of knowledge and complexity of care necessary to offer best therapy to these patients demands a multidisciplinary approach, combining the expertise of cardiology, nephrology, and critical care.

Further research is needed to clarify its pathophysiology and adequate methods of management. Till then individualization of each patient with judicious use of drugs is the best line of management.

Emerging therapies bring hope for better outcomes in these challenging patients.

# ANNEXURES

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**A STUDY OF CHARACTERISTICS AND OUTCOME OF CARDIO RENAL SYNDROME IN HEART FAILURE**

**PROFORMA**

1. Name :
2. Age :
3. Sex :
4. Educational status :
5. Occupation :
6. Address :
7. Telephone No:
8. Height in cms :
9. Weight in kgs :
10. BMI($kg/m^2$)
11. Clinical presentation on admission :
12. Duration of Onset of symtoms :
13. No of previous hospitalisations :
14. NYHA Functional Class:
15. Hypertension : Y / N

    How many yrs: Treatment:
16. Diabetes : Y / N

    How many yrs: Type : Treatment:
17. Hyperlipidemia : Y/N Treatment:

18. Alcohol : Y /N

19. Smoking: Y / N

20. Tobacco chewing: Y / N

21. Sedentary habits:

22. Menstrual H/O:

    a. Premenopausal / Postmenopausal/ Yrs since menopause:

23. **General examination**

    a. Consciousness :

    b. Orientation :

    c. Anemia :

    d. Clubbing :

    e. Icterus :

    f. Pedal edema :

    g. JVP :

    h. Markers of Hypercholesterolemia :

    i. PR : Rate /min

        i. Regular/irregular

        ii. Vessel wall thickening

        iii. Renal bruit

    j. BP : mmHg

    k. RR : / min

    l. Temp:

24. **CVS:**

Apical Impulse:

Heart Sounds:

Added sounds

Murmurs:

**25. RS :**

Air entry:

Adventitious sounds:

26. **P /A :**

Etiology of Cardiac failure :

Duration of hospital stay :

Outcome :

Follow up :

Readmissions if any :

**INVESTIGATIONS :**

1.CBC: TC DC ESR

Hb PCV Platelets

2.RFT :

| | Day 1 | Day2 | Day 3 | Day Disch | 2 months |
|---|---|---|---|---|---|
| Urea | | | | | |
| Creatinine | | | | | |
| Creatinine clearance | | | | | |
| Electrolytes Na | | | | | |
| K | | | | | |

3. FBS

4. PPBS

5. Total cholesterol :

6.Urine R /E : Albumin : Sugar: Deposits:

7. ECG :

8. CXR : Cardiothoracic ratio:

9.ECHO: LVEDD

Systolic Dys: Diastolic Dysfunction:

Peri. Effusion: EF:

10. Ultrasound Abdomen

LK RK

CMD PCS Ascites

11.Thyroid Function Tests(T3, T4, TSH)

**A STUDY OF CHARACTERISTICS AND OUTCOME OF CARDIO RENAL SYNDROME IN HEART FAILURE**

**MASTER CHART**

| No | Ag | Sx | H | W | BMI | PH | NY | HTN | DM | DL | Sm | Alc | HS | Hb | BU | CrD1 | CrD2 | CrDd | CrCD1 | CH | CTR | EF | SD | DD | Re | O |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 65 | M | 170 | 70 | 24.22 | 3 | 4 | N | Y | Y | Y | Y | 10 | 11 | 60 | 3 | 4.4 | 2.1 | 24.3 | 255 | 0.6 | 48 | Y | 2 | 2 | 2 |
| 2 | 48 | M | 160 | 68 | 26.56 | 4 | 4 | Y | Y | Y | Y | Y | 7 | 7 | 40 | 1.8 | 1.5 | 1 | 48.3 | 254 | 0.5 | 50 | N | 1 | 0 | 1 |
| 3 | 16 | M | 150 | 48 | 21.33 | 0 | 3 | N | N | N | Y | N | 8 | 10 | 34 | 1.4 | 0.7 | 0.7 | 59.0 | 154 | 0.55 | 54 | Y | 0 | 0 | 1 |
| 4 | 62 | F | 156 | 65 | 26.71 | 4 | 4 | Y | Y | Y | N | N | 21 | 11 | 49 | 1.5 | 2.5 | 2.5 | 46.9 | 290 | 0.6 | 28 | Y | 2 |  | 4 |
| 5 | 45 | M | 165 | 58 | 21.30 | 2 | 3 | N | N | N | N | N | 7 | 8.5 | 60 | 2.1 | 1.5 | 1.4 | 36.4 | 160 | 0.62 | 49 | N | 1 | 1 | 2 |
| 6 | 50 | M | 157 | 50 | 20.28 | 2 | 4 | N | N | N | Y | N | 21 | 8 | 65 | 1.5 | 1.8 | 1.4 | 41.7 | 150 | 0.6 | 39 | Y | 2 | 2 | 3 |
| 7 | 48 | M | 160 | 65 | 25.39 | 2 | 3 | Y | Y | N | Y | Y | 7 | 10 | 45 | 1 | 1.5 | 1.4 | 83.1 | 210 | 0.5 | 50 | N | 1 | 0 | 1 |
| 8 | 70 | F | 155 | 53 | 22.06 | 4 | 4 | Y | Y | Y | N | N | 6 | 10 | 100 | 4.2 | 3.1 | 5 | 12.3 | 260 | 0.55 | 24 | Y | 1 |  | 4 |
| 9 | 60 | F | 156 | 52 | 21.37 | 2 | 3 | Y | Y | Y | N | N | 12 | 11 | 34 | 1.4 | 1.8 | 1.3 | 41.3 | 220 | 0.53 | 42 | Y | 2 | 1 | 2 |
| 10 | 53 | M | 160 | 50 | 19.53 | 1 | 3 | Y | Y | Y | Y | Y | 15 | 12 | 35 | 1.5 | 2.1 | 1.8 | 40.3 | 287 | 0.6 | 40 | Y | 1 | 1 | 3 |
| 11 | 38 | F | 152 | 48 | 20.78 | 3 | 4 | N | N | N | N | N | 13 | 10 | 56 | 3.1 | 3.7 | 4 | 21.9 | 165 | 0.52 | 30 | Y | 1 |  | 4 |
| 12 | 68 | M | 150 | 65 | 28.89 | 3 | 3 | Y | Y | Y | Y | Y | 11 | 13 | 48 | 1.5 | 1.7 | 1.6 | 43.3 | 286 | 0.55 | 30 | N | 2 | 1 | 3 |
| 13 | 72 | M | 160 | 60 | 23.44 | 2 | 3 | Y | Y | Y | Y | Y | 11 | 10 | 52 | 1.7 | 1.5 | 1.4 | 33.3 | 190 | 0.57 | 38 | Y | 1 | 2 | 3 |
| 14 | 60 | F | 160 | 60 | 23.44 | 3 | 4 | Y | N | N | N | N | 10 | 12 | 64 | 2 | 1.9 | 3.2 | 33.3 | 172 | 0.55 | 26 | N | 2 | 2 | 4 |
| 15 | 54 | M | 162 | 62 | 23.62 | 0 | 3 | Y | Y | Y | Y | Y | 8 | 12 | 36 | 1.8 | 1.7 | 1.4 | 41.1 | 235 | 0.51 | 47 | N | 1 | 0 | 2 |
| 16 | 70 | M | 160 | 58 | 22.66 | 2 | 4 | Y | Y | Y | Y | Y | 12 | 11 | 35 | 1.5 | 1.6 | 1.6 | 37.6 | 197 | 0.59 | 50 | N | 1 | 1 | 3 |

**A STUDY OF CHARACTERISTICS AND OUTCOME OF CARDIO RENAL SYNDROME IN HEART FAILURE**

**MASTER CHART**

| No | Ag | Sx | H | W | BMI | PH | NY | HTN | DM | DL | Sm | Alc | HS | Hb | BU | CrD1 | CrD2 | CrDd | CrCD1 | CH | CTR | EF | SD | DD | Re | O |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17 | 60 | F | 154 | 62 | 26.14 | 2 | 4 | Y | Y | N | N | N | 10 | 10 | 60 | 2 | 3.2 | 3.6 | 34.4 | 186 | 0.59 | 40 | Y | 2 | 1 | 4 |
| 18 | 56 | M | 150 | 50 | 22.22 | 1 | 3 | N | Y | Y | Y | Y | 10 | 10.8 | 47 | 1.4 | 1.8 | 1.3 | 41.7 | 220 | 0.58 | 56 | Y | 1 | 1 | 2 |
| 19 | 40 | F | 160 | 55 | 21.48 | 2 | 4 | N | N | N | N | N | 3 | 10.8 | 62 | 1.2 | 1 | 0.8 | 63.7 | 160 | 0.5 | 52 | Y | 0 | 0 | 1 |
| 20 | 60 | M | 160 | 60 | 23.44 | 0 | 3 | N | N | Y | N | Y | 5 | 11 | 51 | 1 | 0.8 | 0.7 | 66.7 | 210 | 0.5 | 58 | N | 0 | 1 | 1 |
| 21 | 46 | M | 155 | 62 | 25.81 | 2 | 3 | N | N | N | Y | Y | 6 | 11.6 | 35 | 0.8 | 0.7 | 0.7 | 101.2 | 170 | 0.55 | 50 | N | 0 | 1 | 1 |
| 22 | 60 | M | 158 | 60 | 24.03 | 1 | 4 | N | N | Y | N | Y | 6 | 11 | 51 | 0.8 | 0.7 | 0.9 | 83.3 | 220 | 0.6 | 50 | N | 0 | 0 | 2 |
| 23 | 56 | M | 160 | 65 | 25.39 | 1 | 4 | N | N | N | Y | Y | 7 | 11.7 | 31 | 1.2 | 0.9 | 86 | 63.2 | 178 | 0.55 | 58 | Y | 0 | 1 | 1 |
| 24 | 16 | M | 150 | 50 | 22.22 | 1 | 4 | Y | N | Y | N | Y | 5 | 10.2 | 18 | 0.6 | 0.8 | 0.7 | 143.5 | 226 | 0.52 | 43 | N | 1 | 0 | 1 |
| 25 | 61 | M | 165 | 70 | 25.71 | 0 | 3 | Y | Y | Y | Y | Y | 6 | 13 | 19 | 0.7 | 0.8 | 0.8 | 109.7 | 262 | 0.6 | 55 | Y | 0 | 1 | 2 |
| 26 | 38 | M | 162 | 62 | 23.62 | 2 | 4 | N | N | N | N | Y | 8 | 12.5 | 22 | 0.8 | 0.7 | 0.8 | 109.8 | 172 | 0.6 | 47 | N | 1 | 0 | 1 |
| 27 | 55 | M | 170 | 60 | 20.76 | 1 | 3 | Y | Y | Y | Y | Y | 6 | 10.6 | 32 | 0.7 | 0.6 | 0.6 | 101.2 | 285 | 0.55 | 49 | N | 2 | 0 | 2 |
| 28 | 52 | F | 160 | 60 | 23.44 | 1 | 4 | Y | N | Y | N | N | 4 | 9.1 | 38 | 0.6 | 0.6 | 0.7 | 122.2 | 213 | 0.6 | 56 | N | 0 | 0 | 2 |
| 29 | 47 | M | 150 | 50 | 22.22 | 1 | 4 | Y | Y | Y | Y | Y | 6 | 8.2 | 30 | 0.6 | 1 | 0.8 | 107.6 | 210 | 0.53 | 54 | Y | 0 | 1 | 4 |
| 30 | 40 | M | 155 | 62 | 25.81 | 2 | 3 | Y | N | Y | N | N | 7 | 7.2 | 40 | 0.7 | 0.6 | 0.8 | 123.0 | 210 | 0.55 | 52 | Y | 0 | 1 | 1 |
| 31 | 32 | F | 152 | 45 | 19.48 | 0 | 3 | N | N | N | N | N | 7 | 8.5 | 40 | 0.8 | 0.7 | 0.8 | 84.4 | 160 | 0.54 | 54 | N | 0 | 1 | 1 |
| 32 | 45 | F | 160 | 64 | 25.00 | 1 | 2 | Y | N | N | N | N | 6 | 9 | 38 | 0.9 | 0.8 | 0.9 | 93.8 | 165 | 0.58 | 55 | Y | 0 | 1 | 2 |
| 33 | 55 | M | 155 | 60 | 24.97 | 0 | 4 | Y | Y | Y | Y | Y | 7 | 8 | 25 | 1 | 1 | 1.2 | 70.8 | 222 | 0.6 | 48 | Y | 2 | 1 | 1 |

**A STUDY OF CHARACTERISTICS AND OUTCOME OF CARDIO RENAL SYNDROME IN HEART FAILURE**

**MASTER CHART**

| No | Ag | Sx | Ht | W | BMI | PH | NY | HTN | DM | DL | Sm | Alc | HS | Hb | BU | CrD1 | CrD2 | CrDd | CrCD1 | CH | CTR | EF | SD | DD | Re | O |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 34 | 21 | M | 156 | 45 | 18.49 | 1 | 3 | N | N | N | N | N | 7 | 11 | 28 | 1.1 | 1.2 | 0.8 | 67.6 | 145 | 0.55 | 54 | N | 0 | 1 | 1 |
| 35 | 48 | F | 160 | 65 | 25.39 | 1 | 4 | N | N | Y | N | N | 5 | 10.8 | 32 | 0.7 | 0.6 | 0.8 | 118.7 | 250 | 0.5 | 58 | N | 0 | 1 | 1 |
| 36 | 54 | M | 155 | 42 | 17.48 | 1 | 4 | Y | N | Y | N | Y | 10 | 10 | 40 | 0.7 | 0.8 | 0.7 | 71.7 | 210 | 0.6 | 48 | N | 0 | 1 | 2 |
| 37 | 48 | F | 160 | 50 | 19.53 | 2 | 3 | N | Y | N | N | N | 14 | 12 | 45 | 0.6 | 0.6 | 0.8 | 106.5 | 170 | 0.6 | 30 | Y | 1 |  | 4 |
| 38 | 39 | M | 150 | 68 | 30.22 | 0 | 3 | Y | N | Y | N | N | 8 | 14 | 31 | 1.1 | 1.2 | 1 | 86.7 | 300 | 0.55 | 50 | Y | 1 | 1 | 1 |
| 39 | 18 | M | 154 | 50 | 21.08 | 2 | 2 | N | N | N | N | N | 6 | 10 | 40 | 1 | 1 | 1.2 | 84.7 | 159 | 0.54 | 55 | N | 0 | 0 | 2 |
| 40 | 45 | M | 160 | 55 | 21.48 | 0 | 4 | N | Y | N | N | N | 7 | 15 | 45 | 0.7 | 0.7 | 0.8 | 103.7 | 190 | 0.55 | 58 | N | 0 | 0 | 1 |
| 41 | 30 | F | 155 | 53 | 22.06 | 1 | 3 | N | N | N | N | N | 7 | 14 | 38 | 0.6 | 0.8 | 0.8 | 135.0 | 176 | 0.54 | 52 | N | 0 | 0 | 1 |
| 42 | 65 | M | 158 | 60 | 24.03 | 1 | 3 | Y | Y | Y | Y | Y | 6 | 7 | 41 | 0.6 | 0.7 | 0.7 | 104.2 | 224 | 0.58 | 50 | Y | 2 | 1 | 2 |
| 43 | 55 | F | 160 | 55 | 21.48 | 1 | 3 | Y | N | Y | N | N | 8 | 10 | 32 | 0.7 | 0.7 | 0.6 | 92.8 | 234 | 0.6 | 48 | Y | 2 | 0 | 2 |
| 44 | 17 | M | 156 | 48 | 19.72 | 1 | 3 | N | N | N | N | N | 6 | 12 | 22 | 0.6 | 0.8 | 0.8 | 136.7 | 165 | 0.55 | 50 | N | 0 | 0 | 1 |
| 45 | 48 | F | 150 | 50 | 22.22 | 0 | 4 | Y | Y | Y | N | N | 8 | 10 | 30 | 0.6 | 0.6 | 0.6 | 106.5 | 221 | 0.6 | 55 | Y | 1 |  | 4 |
| 46 | 55 | F | 160 | 60 | 23.44 | 1 | 4 | N | N | Y | N | N | 6 | 12 | 41 | 0.9 | 0.9 | 0.7 | 78.7 | 288 | 0.55 | 56 | N | 1 | 0 | 1 |
| 47 | 55 | M | 160 | 55 | 21.48 | 2 | 4 | Y | Y | Y | Y | Y | 8 | 13 | 42 | 0.8 | 0.7 | 0.6 | 81.2 | 220 | 0.6 | 43 | Y | 1 | 1 | 1 |
| 48 | 50 | F | 155 | 55 | 22.89 | 0 | 3 | N | N | N | N | N | 6 | 12 | 32 | 0.6 | 0.7 | 0.8 | 114.6 | 180 | 0.54 | 54 | N | 1 | 0 | 1 |
| 49 | 43 | M | 165 | 90 | 33.06 | 1 | 3 | Y | Y | Y | Y | Y | 10 | 14 | 41 | 0.6 | 0.9 | 0.7 | 202.1 | 320 | 0.52 | 35 | Y | 1 | 1 | 2 |
| 50 | 53 | F | 160 | 45 | 17.58 | 1 | 4 | N | N | N | N | N | 6 | 7 | 23 | 0.6 | 0.7 | 0.6 | 90.6 | 155 | 0.55 | 49 | N | 1 | 0 | 1 |

# KEYS TO MASTER CHART

| | |
|---|---|
| Ag | Age |
| Sx | Sex |
| H | Height |
| W | Weight |
| BMI | Body Mass Index |
| NY | NYHA Functional Class (1= Class I, 2= Class II, 3= Class III, 4= class IV) |
| HTN | Hypertension |
| DM | Diabetes Mellitus |
| DL | Dyslipidemia |
| Sm | Smoking |
| Alc | Alcoholism |
| HS | Duration of Hospital Stay (in days) |
| Hb | Hemoglobin |
| BU | Blood Urea |
| CrD1 | Creatinine on Day 1 |
| CrD2 | Creatinine on Day 2 |
| CrCD1 | Creatinine clearance on Day 1 |
| CH | Serum Total Cholesterol |
| CTR | Cardiothoracic Ratio |
| EF | Ejection Fraction |
| SD | Systolic Dysfunction |
| DD | Diastolic Dysfunction |
| Re | Readmissions |
| O | Outcome (1= complete recovery, 2= partial recovery, 3= persistent symptoms, 4= death) |

# ABBREVIATIONS

| | |
|---|---|
| HF | Heart failure |
| eGFR | Estimated glomerular filtration rate |
| DR | Diuretic resistance |
| ADHF | Acute decompensated heart failure |
| CRS | Cardiorenal syndrome |
| NGAL | Neutrophil gelatinase-associated lipocalin |
| PTH | Parathyroid hormone |
| CCP | Calcium-phosphate product |
| BNP | B-type natriuretic peptide |
| CPK-MB | Creatine phosphokinase-MB |
| ET-1 | endothelin-1 |
| NO-ROS | Nitric Oxide- reactive Oxygen species |
| SNS | Sympathetic nervous system |
| NA/NPY | Noe adrenaline/Neuropeptide Y |
| NF-KB | Nuclear factor kappa B |
| CVP | Central venous pressure |
| CI | Cardiac index |
| WRF | Worsening renal function |
| PCWP | Pulmonary capillary wedge pressure |
| RAAS | Renin-angiotensin-aldosterone system |
| IL | Interleukin |
| TGF | Transforming growth factor |